See related articles on pg 325 and 334

COMMENTARY

Retinoids Putting the "A" in Alopecia

Phillip D. Holler[1] and George Cotsarelis[1]

Vitamin A (vitA) has many roles in human biology. With respect to hair, knockout mice for vitA receptor, hairless, and vitamin D genes have similar phenotypes, and follicle loss occurs during catagen. Hypovitaminosis A from inadequate vitA intake causes hair loss. This work suggests that dietary vitA may have a role in precipitating and maintaining alopecias as well.

Journal of Investigative Dermatology (2013) **133,** 285–286. doi:10.1038/jid.2012.441

Alopecia areata (AA) is a form of nonscarring hair loss resulting from an autoimmune reaction against unknown antigenic components of the anagen hair follicle (Gilhar *et al.* 2012). In contrast, primary cicatricial alopecia (CA) is characterized by relatively nonspecific inflammation, which leads to the destruction of bulge stem cells, follicular scarring, and permanent hair loss (Paus and Cotsarelis, 1999). The etiology of CA is poorly defined, and CA encompasses several distinct diseases with a final common endpoint (Ohyama 2012).

Various lines of investigation into the genetic basis of AA in both humans and animal models have demonstrated a complex, polygenic phenotype, with a dominant influence from the major histocompatibility complex (HLA). Recent large-scale linkage and genome-wide association studies (GWAS) have identified several candidate genes/loci that may have an impact on disease susceptibility (Petukhova *et al.* 2010). Consistent with previous data, the HLA locus showed the strongest genetic effect overall, particularly in the region of HLA class II genes, which are responsible for the presentation of antigenic peptides to $CD4^+$ T cells. Significant associations were also reported for several genes known to modulate the development and/or function of cells of the adaptive immune system, and in particular effector and regulatory T lymphocytes. Taken together, these findings are consistent with the hypothesis that AA results from a breakdown in immune tolerance and that this failure is conditioned, at least in part, by genetic variants that influence the functions of T cells. Interestingly, the GWAS data for AA also associated the risk of disease with the UL 16–binding protein locus, which is known to encode multiple ligands for receptors on NK, NKT, and CD8+ T cells, thus implicating cells of the innate immune system as well.

Large genetic studies provide valuable insights into the molecular pathways controlling the pathogenesis of AA. However, genetic screens of similar scale are not currently feasible for CA. Thus, virtually nothing is known about the genetic control of CA, if it exists at all. In fact, most patients with CA have no family history of the disease, with the possible exception of central centrifugal CA, which occurs with increased incidence in African populations (Olsen *et al.* 2011).

Although the search for susceptibility genes continues, there is mounting evidence that environmental factors such as nutritional status can significantly affect both AA and CA through influences on the hair follicle as well as the activities of various cells mediating autoimmune/inflammatory injury. Notably, minerals such as iron and zinc are important for optimal hair growth, and decreased serum iron has been associated with alopecias in women (Kantor *et al.* 2003). Vitamin A (vitA) and vitamin D promote robust immune responses and have multiple roles in the differentiation and growth of skin, hair, and other tissues (Mora *et al.* 2008).

For decades, dermatologists have used vitA and related compounds (retinoids) to treat a wide range of cutaneous disorders, including psoriasis, acne, and cutaneous T-cell lymphoma. Retinoids function by binding to nuclear receptors, which in turn interact with other transcription factors to coordinate gene expression. The regulation of the retinoid signaling pathway is complex, and retinoids can have numerous effects on multiple tissues in a dose-dependent manner.

The myriad actions of retinoids, as they relate to AA and CA, are the focus of two reports in this issue of *JID* (Duncan *et al.*, 2012; Everts *et al.*, 2012). Using microarray transcriptional profiling of AA lesions in the C3H/HeJ mouse model, Duncan *et al.* 2012 showed that genes involved in retinoid metabolism are upregulated in AA lesions compared with controls, a finding that was supported by histochemical analysis of human, mouse, and rat tissues. C3H mice that were fed diets containing a range of vitA levels (up to 7× normal) showed increased hair loss in cohorts receiving high, but not excess, levels of vitA, and mice fed diets low or deficient in vitA also trended toward worse alopecia. Low vitA diets correlated with increased numbers of infiltrating lymphocytes, epidermal hyperplasia, and dystrophic follicles. Interestingly, mice fed excess vitA were relatively protected from alopecia. The authors noted increased anagen follicles in the high and excess vitA groups, although whether this was primary to vitA or secondary to epidermal changes is not clear. Further analyses demonstrated differences in the frequencies of granzyme B^+ cells, as well as levels of cytokines among the various cohorts,

[1]*Department of Dermatology, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania, USA*

Correspondence: George Cotsarelis, Department of Dermatology, University of Pennsylvania Medical Center, 211 CRB, 415 Curie Boulevard, Philadelphia, Pennsylvania 19104, USA.
E-mail: cotsarel@mail.med.upenn.edu

Clinical Implications

- Nutritional factors influence development of alopecia.
- Vitamin A levels may relate to onset of cicatricial alopecias.
- Vitamin A levels may affect alopecia areata.

although these differences were not consistent across all time points.

Mice lacking vitA receptor, vitamin D receptor, or hairless, lose hair permanently, as the follicle disintegrates during catagen. The hair follicle stem cell population remains, but the hair follicle dermal papilla detaches from the stem cells and prevents mesenchymal–epithelial interactions necessary for hair follicle cycling. Whether deficiencies in ligand (vitA or vitamin D) cause related defects is not clear, but two papers in this issue raise this possibility.

Intriguingly, recent work by the Karnik group showed that an inhibitor of cholesterol synthesis may induce catagen and lead to CA (Panicker *et al.* 2012). This raises the possibility that induction of catagen in large numbers of follicles, perhaps as seen in telogen effluvium, may trigger alopecias.

Using the C57Bl/6 mouse model of CA as well as human samples, Everts *et al.* 2012 demonstrated that genes involved in retinoid pathways were upregulated in mild CA, but were undetectable in late-stage disease. Feeding studies utilizing diets with normal, high, and excess vitA revealed a complex relationship between retinoids and CA. In one set of experiment, mice receiving excess vitA diets were protected from alopecia, follicular dystrophy, and inflammation. However, a second set of feeding experiment showed that the high vitA dose was protective in mice that had been previously raised for two generations on a vitA-deficient diet to deplete liver stores, suggesting a tight optimal dosage window that may be altered by polymorphisms in the *ADH7* gene.

Together, these reports highlight the potential importance of a nutritional factor, vitA, in the pathogenesis of AA and CA, but the precise mechanism behind these effects remains unclear and requires further investigation. More generally, these results illustrate how the complex interplay between genes and environment may affect diseases in multiple ways. The precipitating factors or ''triggers'' in AA and CA are unknown but may include aberrant responses to trauma, infection, medication, or other stresses (Figure 1). Predisposing factors, such as genetics and nutrition, likely do not incite inflammation but instead act in concert to set the threshold for initiating and/or propagating disease. It is noteworthy that trauma due to tension on the hair is thought to have an important role in certain types of CA in humans. However, Everts *et al.* (2012) report that plucking in the B6 model did not provoke CA. The reason for this discrepancy is not clear but could result from differences between mouse and human hair follicles (i.e., more telogen follicles in mice vs. humans). It would be interesting to know whether plucking anagen hairs produced a different result.

In extrapolating the authors' findings to other disorders of the skin, hair, and epithelia, it would be prudent for investigators to assess the potential impact of retinoids on their experimental systems and to consider controlling for vitA intake and other nutritional parameters to avoid confounding effects.

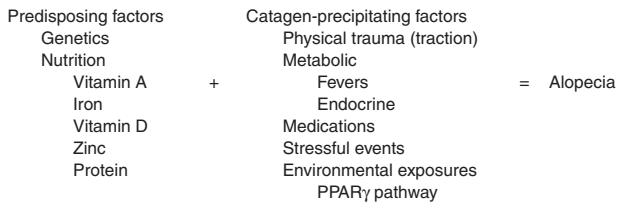

Figure 1. Two-step hypothesis of hair loss.

CONFLICT OF INTEREST
The authors state no conflict of interest.

REFERENCES

Duncan F, Silva K, Johnson C *et al.* (2012) Endogenous retinoids in the pathogenesis of alopecia areata. *J Invest Dermatol* 133:325–33

Everts H, Silva K, Montgomery S *et al.* (2012) Retinoid metabolism is altered in human and mouse cicatricial alopecia. *J Invest Dermatol* 133:334–43

Gilhar A, Etzioni A, Paus R (2012) Alopecia areata. *N Engl J Med* 366:1515–25

Kantor J, Kessler LJ, Brooks DG *et al.* (2003) Decreased serum ferritin is associated with alopecia in women. *J Invest Dermatol* 121:985–8

Mora JR, Iwata M, von Andrian UH (2008) Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat Rev Immunol* 8: 685–98

Ohyama M (2012) Primary cicatricial alopecia: recent advances in understanding and management. *J Dermatol* 39:18–26

Olsen EA, Callender V, McMichael A *et al.* (2011) Central hair loss in African American women: incidence and potential risk factors. *J Am Acad Dermatol* 64:245–52

Panicker SP, Ganguly T, Consolo M *et al.* (2012) Sterol intermediates of cholesterol biosynthesis inhibit hair growth and trigger an innate immune response in cicatricial alopecia. *PLoS One* 7:e38449

Paus R, Cotsarelis G (1999) The biology of hair follicles. *N Engl J Med* 341:491–7

Petukhova L, Duvic M, Hordinsky M *et al.* (2010) Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. *Nature* 466:113–7