New developments in hair research (Editorial - Letter)

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ABSTRACT

This article is an editorial for the special focus theme issue on "hair research" published by the Experimental Dermatology journal. Here we introduce the articles from the special issue and pose a few questions. The full list of publications for the hair research special issue is available on the Journal's web site. Many of the articles can be viewed free of charge on the web site. This is for; Experimental Dermatology, Volume 29, Number 3, published March 2020.

INTRODUCTION

The hair follicle is a highly complex organ, the biology[1, 2] and chemistry[3,4] of which has greatly exercised the minds of scholars, including some of the greatest minds (see below).[5] Consequently, the field of hair research has progressively expanded over the years. Using the National Institutes of Health (NIH), journal periodicals database, a simple search for the keyword "hair" reveals a significant increase in publications from less than 10 articles per year at the beginning of the 20th Century to over 1800 in 1999. So far in the new millennia, the number of hair related journal reports has further improved with over 4000 publications in 2019 alone. Over the years, *Experimental Dermatology* has proudly contributed to this renaissance of hair research, for which just a few selected papers from 2018 to 2019 may serve as *pars pro toto*, indicating also the interdisciplinarity of this research arena and the enormous spectrum of topics the field covers today.[6–8]

The arena of hair research is still comparatively small, but fast-growing, and it continues to garner increasing interest from a wide range of scientists, clinicians and the general public. Therefore, in this Focus Theme Issue, we have assembled reviews, opinions and original research from the many diverse niches of the hair research world. Several examine aspects of essential hair biology, others con-sider the consequences of alterations in hair follicle function leading to hair loss, and some look to how these adverse effects can be com-bated with select therapies. A few comments may suffice to guide the reader through this kaleidoscope of current research activities.

ALOPECIA AREATA

Alopecia areata (AA) as a non-scarring alopecia, has held the attention of physicians and those afflicted for at least 3500 years and probably for much longer. In the context of George Santayana's famous quote; "Those who cannot remember the past are condemned to repeat it", Broadley and McElwee's review of AA history provides a reminder that long-forgotten research investigations contain information still relevant today.[9] Of particular note, Giovannini's detailed histological investigation of AA, his identification of follicular inflammation, and conclusion that inflammatory cells likely drove alopecia, was 70 years ahead of its time.[10] If Giovannini's work had been given credence at the time of publication in 1891, would our knowledge of AA be more advanced today?

Diffuse AA was only identified as a distinct diagnosis in 1945,[11] but it has perplexed many over the years since. Zhang et al, present a detailed investigation into the progression of diffuse AA by examination of hair roots.[12] They confirm that diffuse AA is initially an anagen effluvium, only later progressing to a telogen effluvium pattern of hair loss. If so, then the inflammation observed in diffuse AA is an intense and simultaneous infiltration of select hair follicles across the scalp. This sudden onset, widespread, yet selective, follicular inflammation does not sit well with hypotheses of AA progression by “wave or ripple-like” expansion and migration of alopecic lesions over the skin.[13,14] One wonders if it is truly an alopecia “areata”, or might it be better identified as a distinct non-scarring alopecia?

Zhang and colleagues also examine cytokine expression in AA patients undergoing treatment with diphencyprone (DCP) and conclude that patients exhibiting high levels of IL-4 in their blood are less likely to respond to treatment.[15] The response to contact sensitizing agents is variable, while some patients produce an excellent response, DCP fails to promote hair growth in others. The data indicate that patients with a more Th2 type cytokine profile may not be suitable candidates for contact sensitization treatments. The variable Th1, Th2 cytokine profile of AA patients also suggests there may be variation in the underlying disease pathogenesis for different individuals. Previously, Ikeda proposed several subtypes of AA including “atopic AA” driven or modified in part by allergy responses.[16] Zhang and McElwee expand on this view and summarize evidence that supports the existence of atopic AA.[17] If there are variations in the mechanisms underlying AA pathogenesis, treatment approaches may need to be tailored to the individual based on their disease activity profile.

Petukhova et al provide data suggesting a significant role for autophagy in AA development.[18] Kang et al, provide some initial insight into a potential role for toll-like-receptor signalling in AA.[19] Herz-Ruelas et al, examine the secretion of stress hormones in AA in response to ultra-violet A (UVA-1) phototherapy.[20] These studies suggest that we need to look well beyond the lymphocyte infiltrate and investigate the role of the innate immune system, and the dynamics of hair follicle biology, to fully understand the mechanism(s) of AA pathogenesis as well as the responses to treatment. In doing so, we may discover new mechanisms that promote hair loss and signalling systems that could be targeted in developing more effective treatments.

In the longer term, one of the key objectives for AA research is to discover new therapies. To this end, Kim and colleagues present a study investigating the potential for mesenchymal stem cells to protect dermal papilla cells under inflammatory stress.[21] Cell therapies are in development for many chronic conditions where there is a deficit in tissue formation and/or a pro-inflammatory environment and AA may be a further candidate. While immuno-suppressive drugs are the most obvious candidates for development into new treatments for AA, one can never be sure with AA. For example, 2-deoxy D-Glucose shows promise for treating autoimmune diseases such as systemic lupus erythematous, but the treatment had no significant

effect in an AA mouse model.[22]Treatments with multiple modes of action, as with cell therapy, may be more effective for AA.

SCARRING ALOPECIA

There are some parallels between progress in research on AA and the scheme of scarring alopecias. While much research has traditionally focused on the role of lymphocytes in both scarring and non-scarring hair loss, scholars are now beginning to look beyond the immediate adaptive immune system paradigm.[23] Hobo and col-leagues reveal mast cells are present in large numbers in the inflammatory lesions of lichen planopilaris (LPP). These cells also express IL-17 and IL-23 which may support lymphocyte activation and/or changes to hair follicle biology.[24] Innate cells, non-immune cells, extracellular matrix remodelling,[25] cytokines, chemokines and hormones in the vicinity may all have an impact on the development of lymphocytic scaring alopecias.

Doche and colleagues demonstrate that perifollicular lymphocytic inflammation can be observed in overtly unaffected scalp skin of LPP and frontal fibrosing alopecia (FFA) patients.[26] The data suggest a much more generalized inflammation is present, extending well beyond the lesion limit. As such, the question arises, what determines the onset of overt alopecia? Is it simply an issue of lymphocyte accumulation and a need reach beyond a threshold level of inflammation intensity for alopecia to develop? Or is it due to a progressive capitulation of any putative immune privilege resistance mechanisms? And/or something else in the local environ that decides where lesions will develop? In fact, Doche et al also characterize the presence of neurogenic inflammation in LPP and FFA both within and beyond the alopecic lesions.[27] They observed differences in neuropeptide distribution, in LPP versus FFA. The variable presence of these neuropeptides begs the question, do they have a significant role to play in promoting clinically overt alopecia and the location of lesions?

Polak-Witka et al review the role of the microbiome in hair follicle biology and disease.[28] How microbes interact with the immune system and how they might elicit immune responses in the vicinity of hair follicles may be important for understanding skin and hair conditions including psoriasis, androgenetic alopecia and alopecia areata, but it is particularly relevant for

understanding folliculitis decalvans (FD). Matard and colleagues reveal a persistent, abnormal subepidermal microbiota is present in FD, both in lesional skin and also in non-lesional skin.[29] Here too, subtle variations in microbiota composition and/or intensity of colonization, in different locations in the scalp skin, could alter the nature or strength of inflammatory cell signalling to define the distribution of lesions on the scalp. Subash et al review the research into central centrifugal cicatricial alopecia (CCCA) and compare and contrast the cicatricial alopecia to LPP and other scarring diseases.[30] They suggest a genetic predisposition could prime scalp hair follicles to CCCA, but additional factors are needed to trigger a lymphocytic autoimmune response and induction of the clinical disease.

This principle may be applicable to many forms of inflammatory alopecia; an underlying genetic predisposition, overlaid by one or more triggers for onset, with local modifiers of disease intensity determining the location of lesions, produces the observed clinical phenotype. One possible underlying predisposing factor for scarring alopecia susceptibility, and/or trigger for onset of the disease, may be derived from cholesterol biosynthesis. Palmer and colleagues review the expression and activity of cholesterol synthesis and function in hair follicles and how the system may be involved in cicatricial alopecias as well as other skin and hair loss conditions.[31] In addition, one might also consider the potential role of cholesterol production by lipoautophagic dermal adipocytes adjacent to hair follicles.[32] A mechanism of influence on cholesterol synthesis comes from the peroxisome proliferator-activated receptors (PPAR) family of ligand-activated nuclear receptors. PPARγ is significant in keratinocyte differentiation and can influence hair cycling and inflammatory responses. Ramot and colleagues review the PPAR family, particularly PPARγ, and its function in hair follicles.[33] Beyond a role in scarring alopecia, they also consider the potential for PPARγ interaction to be active in androgenetic alopecia and hirsutism.

HAIR BIOLOGY

Inflammation has long been recognized as a primary driver of non-scarring and scarring alopecias, but more recently, research studies have shown that cells of the innate and adaptive immune systems may also play a role in regulating and modifying the nor-mal hair cycle. Wang and Higgins review the evidence to date and consider the mechanisms of immune cell influence

over hair growth and hair loss.[34] Perifollicular mast cells, γδ T cells, natural killer cells and macrophages are understood to affect hair growth cycles via secretion of hair follicle-targeting growth factors.[35]Interestingly, recent studies suggest another mode of action by which cells may signal to each other. Exosomes derived from cultured dermal papilla cells could be used to induce trichogenicity of dermal papilla cells in a hair reconstitution assay.[36] One wonders whether exosomes from infiltrating inflammatory cells may signal to hair follicles, in addition to chemokine and cell receptor-ligand signalling?

Studies on hair biology have defined many modifiers of hair follicle structure and functioning. Unsurprisingly, growth factors play a significant role in the development and maintenance of hair follicles.[37] This knowledge has been adapted in different ways in studies to develop new treatment approaches for hair loss. Siah et al focus on platelet-rich plasma (PRP) and compare and contrast the concentration of several growth factors in PRP taken from different patients over time.[38] That concentrated PRP could have a positive impact on hair growth makes sense, given the enrichment in growth factors. However, the significant variability in PRP quality between different individuals suggests there is more work to do in standardizing and improving PRP for use in treating androgenetic alopecia and other forms of hair loss.

In contrast, a much simpler approach would be to identify exogenous factors that can be developed into treatments to promote hair growth. Bak and colleagues show that Boehmite has potential for promoting hair growth through inducing cell signalling and activation of anagen.[39] Boehmite is an aluminium oxide hydroxide with a number of industrial purposes that is currently being investigated as a vaccine adjuvant.[40] Perhaps, it may yet find a new role via its apparent cell growth and inflammatory modulating properties.[41] Pantelireis and Higgins argue that therapies for treating hair loss should be developed which can alter dermal papilla size, rather than just promote hair growth.[42] Bak et al show Boehmite promotes the β-catenin path-way and increases expression of vascular endothelial growth factor (VEGF), both associated with increasing dermal papilla and overall hair follicle size in previous studies. Might Boehmite and/or other treatments with similar effects facilitate dermal papilla regeneration?

Ultimately, treatment for alopecia should not only promote hair growth from existing follicles, but also attempt to generate new follicles to replace those lost, or even to increase density for those with naturally thin hair. Leng et al have developed an in vivo assay of cell trichogenicity called “the punch assay”.[43] Using dissociated cells from both mice and humans, they demonstrate skin can be fully re-constituted with incorporation of hair follicles, though use of human cells was less effective compared to mouse cells. This assay, together with related methodologies,[44–46] may be a simple, attractive sys-tem for use in developing future clinical applications. Not least, one might be able to investigate whether injury conditioned human dermal stem cells would prove more trichogenic in this assay system,[47] and/or whether bulge stem cells exposed to chemotherapy and radiotherapy injury are less effective.[48,49] It may also be possible to use these techniques to test the consequences of genetic mutations in different cell types,[50, 51] and/or to evaluate whether extracellular factors can modify trichogeneicity.[52]

Carré et al consider the role of hair follicles and their production of hair fibre in a rather different light. While hair fibre is well recognized for its role in skin protection and social communication, they ask whether hair follicles can be viewed as waste processing plants, assisting in the neutralization and removal of toxins from the body.[53]As such, hair fiber could be described as an excreted waste product, an idea that was first put forward by Aristotle. He claimed that “gross humors” purged and evacuated from the brain, pass through pores in the skin, dry and harden into hair.[5] Wortmann and colleagues consider the question “why is hair curly”?[54] Following up from their previous work on cortical cell fractions,[55] the authors examine cell proliferation and segregation, as well as the spatial and time dynamics that contribute to hair curl. Here too, Aristotle had something to say; “the cause of the curling of the hair is great abundance of heat”; in contrast, straight hair is “due to an abundance of gross humors”. And in case you were wondering, Aristotle also claims that humans have the longest scalp hair of all living creatures because we have the “moistest brains”.[5] On this rather speculative note, we conclude our introductory comments to this Focus Theme Issue. We hope the reader will derive as much stimulation and education from it as we did when putting it together.

KEYWORDS

hair biology, hair research, alopecia areata, scarring alopecia

ABBREVIATIONS

AA alopecia areata; CCCA central centrifugal cicatricial alopecia; DCP diphencyprone; FD folliculitis decalvans; FFA frontal fibrosing alopecia; IL− Interleukin−; LPP lichen planopilaris; NIH National Institutes of Health; PPAR peroxisome proliferator-activated receptors; PRP platelet-rich plasma; VEGF vascular endothelial growth factor

CONFLICTS OF INTEREST

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