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VIEWPOINT

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# A niche in the spotlight: Could external factors critically disturb hair follicle homeostasis and contribute to inflammatory hair follicle diseases?

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## Abstract

The anatomy of the hair follicle and the dynamics of its barrier provide a special space for interactions between macromolecules and the underlying tissue. Translocation across the hair follicle epithelium and immune recognition has been confirmed for proteins, nucleic acids, engineered particles, virus particles and others. Tissue responses can be modulated by pro-inflammatory stimuli as demonstrated in penetration and transcutaneous immunization studies. Even under physiological conditions, hair follicle openings are filled with exogenous material ranging from macromolecules, engineered particles to natural particles including diverse communities of microbes. The exposed position of the infundibulum suggests that local inflammatory insults could disturb the finely tuned balance and may trigger downstream responses that initiate or facilitate local outbreaks of inflammatory hair diseases typically occurring in close spatial association with the infundibulum as observed in cicatricial alopecia. The question as to how microbial colonization or deposition of contaminants on the surface of the hair follicle epithelium interact with the barrier status under the influence of individual predisposition may help us understand local flare-ups of inflammatory hair diseases. Specifically, learning more about skin barrier alterations in the different types of inflammatory hair diseases and cross-talk with exogenous compounds could give new insights in this less explored aspect of hair follicle homeostasis. Such knowledge may not only be used to develop supportive measures to maintain a healthy scalp. It may have wider implications for our understanding on how external factors influence inflammation and immunological responses in the skin.

KEYWORDS

alopecia, bulge region, microbiome, nanoparticle, transcutaneous vaccination

## 1 | INTRODUCTORY OVERVIEW

The hair follicle is increasingly recognized as an important regulator of cutaneous regeneration and immunity. Its complex organization fascinates researchers from a wide range of disciplines including medicine, developmental biology, genetics, stem cell research, neurobiology, immunology and bioengineering. Among these different fields of interest, its prominent role as interface for interactions between exogenous compounds and the cutaneous immune system deserves a closer look. In reference to its anatomic position, it is frequently referred to as "niche". Yet, recent insights from different directions suggest that this term greatly underestimates the profound effects that immunological alterations have on the function of the hair follicle itself, on cutaneous immune cells and on the generation of systemic immune responses.

Even under physiological conditions, hair follicle openings are filled with exogenous material ranging from macromolecules, engineered particles to natural particles including diverse communities of microbes. The question as to how microbial colonization or deposition of contaminants on the surface of the hair follicle epithelium interacts with the barrier status under the influence of individual predisposition and local effects may help us understand local flare-ups of inflammatory hair diseases. Specifically, learning more about skin barrier alterations in the different types of inflammatory hair diseases and cross-talk with exogenous compounds could give new insights in this less explored aspect of hair follicle homeostasis. Such knowledge may not only be used to develop preventive and supportive measures to maintain a healthy scalp. It may have wider implications for our understanding on how external factors influence inflammation and subsequent local and systemic immunological responses.

## 2 | BACKGROUND

### 2.1 | Specific anatomical features facilitate interactions across the hair follicle epithelium

Stimulated by previous work on the penetration of topically applied particles and macromolecules,[1,2] we recently encouraged investigations on the microbial colonization of the hair follicle and on how alterations in the distribution of microbes along the hair follicle epithelium may be involved in the triggering of inflammatory responses and the propagation of inflammatory hair diseases.[3] This proposition was based on the fact that the funnel-shaped infundibulum provides a space that, in the case of scalp terminal hair follicles, extends deep into the dermis. This opening is not only typically filled with microbes, but also serves as a reservoir and a penetration pathway for a wide range of exogenous compounds.

Small molecules, as shown for caffeine[4] (MW 194 g/mol) and minoxidil[5] (MW 209 g/mol), effectively use this pathway via the hair follicle for shunt penetration. When applied on the scalp of human volunteers, minoxidil became detectable in blood samples within 5 minutes, while closure of hair follicles resulted in a 30-minute delay.[5] The fact that the penetration occurs via the follicular canal was demonstrated ex vivo in a diffusion cell model using human scalp skin,[6] but the exact penetration pathway remains less clear. The change of the differentiation pattern from a typical epidermal keratinization to a tricholemmal differentiation in the area of the entry level of the sebaceous duct suggests that this part of the lower infundibulum is a key site for interactions between exogenous compounds and the underlying tissue.[7] While follicular tight junctions in the superficial part are expressed complementary to the stratum corneum, they eventually remain the only barrier and are being lost towards the bulb.[8] Nonetheless, tight junction proteins are expressed within the outer root sheath of the upper and central isthmus regions and in the companion layer at the border of the outer and the inner root sheath.[9] Functionally, however, outer root sheath keratinocytes collected from anagen hair follicles from cheek and forehead skin exhibited weaker tight junction activity than keratinocytes from interfollicular epidermis as assessed by trans-epithelial resistance.[10] Additionally, the barrier formation in anagen hair follicle keratinocytes was less tight than that in regular scalp epidermis.[10]

The exposure time of the tissue to small molecules is typically short, because the high vascularization provides effective drainage, whereas macromolecules and particulate matter get trapped. The hair fibre stabilizes the opening,[11] provides guidance and eventually retains such compounds,[12] which remain there in close contact with the epithelium even in the presence of sebum flow.[13] Against the expectation that macromolecules cannot pass the skin barrier,[14] the deeper parts of the infundibulum were shown to be key sites for immune recognition. Most knowledge has been generated from studies, in which model compounds or therapeutic macromolecules and particles were applied on the surface of hair follicle-bearing skin.[2,15] Some studies, however, addressed the penetration of natural particles including pollen allergens,[16] as well as unintended exposure to particulate matter in air pollution[17] and different applications of metal particles.[18]

### 2.2 | Macromolecules and particles get access to viable skin tissue via hair follicles

Following early reports on size-dependent penetration[19] of particles along the hair follicle duct,[20,21] the fact that hair follicles are sites where translocation of macromolecules takes place has been further confirmed in a range of different model systems. Just recently, in a series of experiments using nano-emulsions of different sizes, Su et al demonstrated that they filled the hair follicle canal and released their cargo in the surrounding dermal tissue. Consistent with our own previous observations,[21] mean particle sizes of 500 nm remained on the epithelium while smaller particles sizes below 200 nm could increasingly be identified in the underlying tissue with indications of uptake by antigen-presenting cells.[22] The data are in accordance with flow cytometric analyses on the skin penetration of 200 nm and 500 nm nanoparticles by our group[23]

and our observation that core-multi-shell nanocarriers passed the hair follicle epithelium and were taken up by antigen-presenting cells.[24] Similarly, macromolecular vaccine compounds based on protein[25] and even nucleic acids reach the cutaneous immune system via hair follicles, especially when targeted in the anagen phase.[26,27] Successful transfection of cells in the deeper hair follicle was achieved with DNA plasmids applied in liposomal formulation.[28-30] Complementary to those results, in vivo studies in mice tracked the trafficking of particles from the skin, along the hair follicles, to draining lymph nodes, and illustrated the distribution and cellular uptake of virus particles along the hair follicle epithelium.[31]

## 2.3 | The hair follicle plays a key role in the mediation of local and systemic immunological responses

Technically, keratinocytes and epidermal Langerhans cells (LCs) are the first cell populations that come in contact with material that translocates across the skin barrier. As one typical example, metal oxide nanoparticles which accumulated in skin furrows and hair follicles[32] were shown to trigger inflammation via induction of reactive oxygen species,[17,33] resulting in cytokine production by keratinocytes capable of recruiting immune cells. For metal nanoparticles, ion release, barrier passage and concomitant induction of metal ion-specific CD4+ T-cell and IL17-mediated immunoreaction have been reported.[34]

But the keratinocyte activation also contributes directly to the uptake of exogenous material by LCs, which is typically accomplished by dynamic interactions of LC dendrites with the tight junctions that connect keratinocytes. Those tri-cellular contacts enable LCs to reach out to superficial compartments and gain access to external antigens[35] (Figure 1). The presence of activating stimuli further enhances such uptake capacities, as shown in ex vivo skin explant models.[21,23] Even minor barrier insults by mechanical, chemical or pro-inflammatory biochemical stimuli were capable of putting keratinocytes and antigen-presenting cells in an activated state that facilitated antigen uptake and recognition of larger molecules by antigen-presenting cells across the skin barrier.[35] Despite the exposed position of LCs and keratinocytes, several investigations on the cellular uptake of topically applied antigen[36] or nanogels[37] indicate that dermal dendritic cells are also among the initial responders to penetrating compounds, which is in line with their established role as effectors for the induction of systemic immune responses.[38] As a consequence, targeting of vaccine compounds to hair follicles was proposed as an effective strategy for transcutaneous vaccination.[23,39,40]

In clinical studies using a transcutaneous vaccination method which targeted vaccine compounds towards hair follicles,[21,23] the transcutaneous administration of protein-based influenza vaccine in healthy human volunteers and HIV-infected individuals confirmed that such targeting of vaccine to hair follicles allowed to effectively reach dendritic cells. Interestingly, this vaccination route preferentially shaped CD8-cytotoxic responses.[41,42] When DNA vaccine encoding a

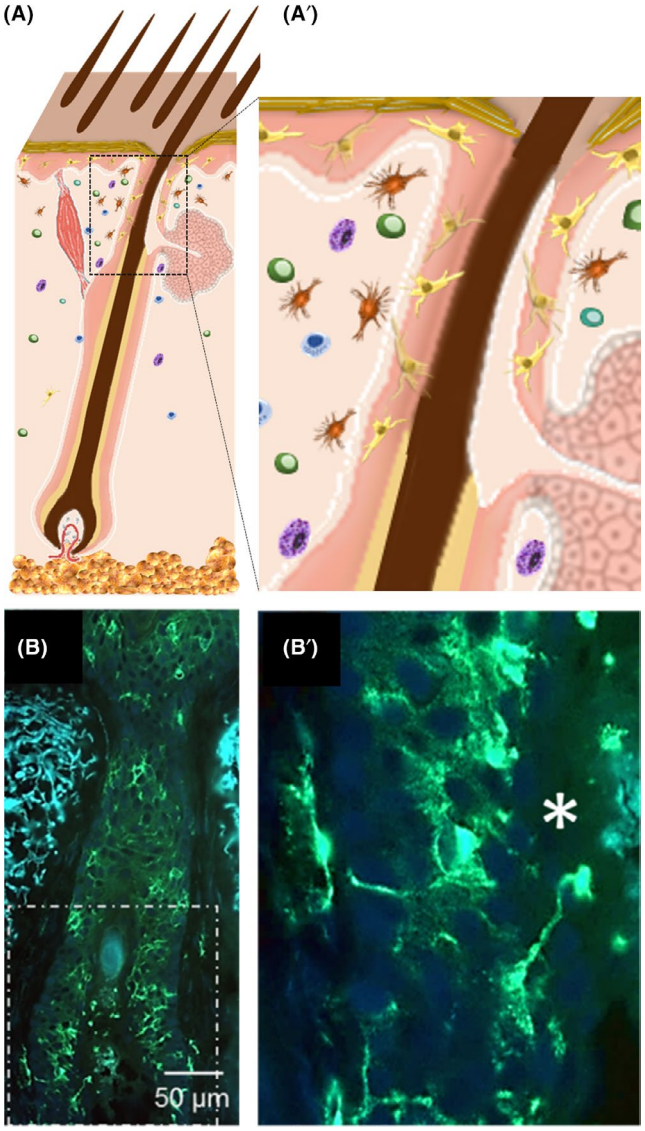


**FIGURE 1** The role of the hair follicle infundibulum as reservoir and interface is well established (A, A'). The immunfluorescence staining of human hair follicle (anti-CD1a) illustrates the dendriticity of Langerhans cells (LC) residing in the hair follicle epithelium and the short distance between dendrite extrusions (*) and the lumen as indicator for ongoing scanning activities at this interface, although LC are clearly not the only key players in this complex interplay (B')

Multi HIV B clade fusion protein (GTU®MultiHIV B clade) was administered to HIV clade B positive individuals via intramuscular injection, addition of one fifth of the dose as transcutaneous application making use of hair follicles as vaccine entry portal shifted the response towards a TH17-dominant immune response,[43,44] which fits into the role of IL17a induction as a key pro-inflammatory cytokine involved in T-cell activation, tissue inflammation and memory responses.[45] In accordance with those investigations, immune profiling of individuals vaccinated with a vaccine based on Modified Vaccina Ankara virus, a vector previously shown to enter the hair follicle epithelium in mice,[31] revealed that this same transcutaneous vaccination procedure induced IL-17 in the serum which was concomitant with CD8-type responses assessed at day 28 after vaccination.[46]

Those investigations illustrate that immunological cross-talk at the barrier of the hair follicle epithelium does not only affect the surrounding tissue, but also contributes to the shaping of systemic immune responses.

While the direct capacity of LCs to cross-present antigen is increasingly questioned, LCs appear to be involved in the acquisition of effector functions of CD8+ T cells that infiltrate the skin during Toll-like receptor-mediated inflammation.[47] In humans, LCs but not dermal DCs constitutively promoted local proliferation and activation of skin resident memory CD4+ T reg, after infection with Candida albicans in the absence of antigen.[38] In addition, LCs seemed necessary and sufficient to induce immunity to yeast (Candida albicans) and extracellular bacteria (Staphylococcus aureus) by promoting induction of TH17 cells,[48] which is in line with the concept that, upon sensing environmental insults, LCs contribute to the mounting of TH17 type responses.[49] In fact, production of inflammatory cytokines, specifically IL1-beta, IL-6, IL-23 and TGF-beta, has been proposed as dendritic cell-derived additional signal for the induction of TH17 responses.[50]

Those studies link cross-talk and responsiveness to typical commensals of the hair follicle epithelium, to the uptake events that occur at the barrier. Downstream effects on the underlying tissue, however, vary depending on the type of stimulus and the microenvironment. An uptake by different dendritic cell subsets through the hair follicle in the absence of adjuvant, for example, has been implicated in the generation of immune tolerance.[51]

Further studies are necessary to understand changes in the skin microenvironment in response to external stimuli as it has been done by proteomic analysis,[52] but the experimental exploration is complicated by the number of variables which determine the outcome of hair follicle exposure to exogenous compounds. Besides the skin barrier and the tissue environment, the hair cycle has a profound impact on the accessibility and the responsiveness of the hair follicle-associated immune system. For example, penetration of liposomal ovalbumin via hair follicles on murine skin[53] was more effective when hair follicles were put in anagen stage.[27] Li et al found that immunogenicity of topical DNA application was significantly enhanced when hair follicles in the application area were induced into anagen stage by hair plucking, presumably because transfection rates typically occurred at the onset of a new growing stage of the hair cycle.[54] On the other hand, depression of delayed type hypersensitivity reactions was observed in mice when hair follicles were synchronized in anagen.[55]

## 3 | COULD DYSREGULATED CROSS-TALK AT THIS INTERFACE CONTRIBUTE TO INFLAMMATORY HAIR DISEASES?

The characteristic distribution of immune cells along the follicle reflects a compartmentalization into areas of enhanced infiltration, typically around the infundibulum, and protected areas largely devoid of immune cell infiltrates.[56] The distribution of the different immune cell subsets is not random, but the result of well-orchestrated interactions between keratinocytes and immune cells mediated by a highly compartmentalized expression of chemokines, for example, CCL20 in infundibulum cells shifting to CCL2 in the isthmus area.[57] The exposed position of the infundibulum suggests that local inflammatory insults could disturb this finely tuned balance and may trigger downstream responses that initiate or facilitate local outbreaks of inflammatory hair diseases typically occurring in close spatial association with the infundibulum as observed in cicatricial alopecia (Figure 2A). Only few studies are available on the role dendritic cells in alopecia. Flamm et al recently described increased numbers of LCs extending into the lower hair follicle in central centrifugal cicatricial alopecia.[58] Enhanced LC/T lymphocyte ratios were reported in lichen planopilaris compared to traction alopecia,[59] while a loss of LCs in interfollicular epidermis was described in association with hair follicle destruction in lichen planopilaris and folliculitis decalvans.[60] Perifollicular and intrafollicular LCs appear to be increased in hair follicle affected the frontal fibrosing alopecia,[61] but most investigations are limited to immunohistochemical stainings of patient biopsies.

Only few studies specifically address components on the outer surface of the hair follicle epithelium in the context of alopecia, and mostly relate to microbial colonization. Hybridization and immune fluorescence microscopy in healthy facial skin revealed a mix of bacterial and fungal communities, which were unevenly distributed but showed physical attachment to the epithelial surfaces, in many cases embedded in complex extracellular matrix with biofilm formation.[62] Given that bacteria typically exceed the size of one micron, it appears more likely that signalling occurs via receptor-mediated recognition, for example, toll-like receptors, breakdown products or metabolites as shown in acne vulgaris.[63,64] In the neutrophilic scarring alopecia folliculitis decalvans, biofilm formation along the hair follicle and the abnormal subepidermal microbiota is acknowledged as critical factors for the chronic persistence and recurrent flare-ups of this type of alopecia.[65] Interestingly, presence of Staphylococcus aureus in scalp skin of folliculitis decalvans patients increased the chance of subepidermal colonization,[66,67] pointing towards the possibility of translocation of bacteria across inflamed skin barriers.

The question as to whether external factors contribute to onset and propagation of lymphocytic scarring alopecia, such as lichen planopilaris, is less explored despite the fact that local mechanical or biochemical inflammatory stimuli are recognized contributors to lichen-type inflammation although rarely described in scalp skin.[68,69] Compared to folliculitis decalvans, few is known on the microbial colonization of hair follicles affected by this alopecia entity.

In contrast, the peculiar clinical pattern of frontal fibrosing alopecia, an alopecia entity with increasing incidence that exhibits similar histopathologic features as lichen planopilaris, recently stimulated more specific research on a possible role of external factors.[70] Following epidemiological investigations that pointed towards an association with the use of cosmetics and specifically sunscreen products, first attempts have been made to confirm this hypothesis experimentally. Preliminary data on the deposition of

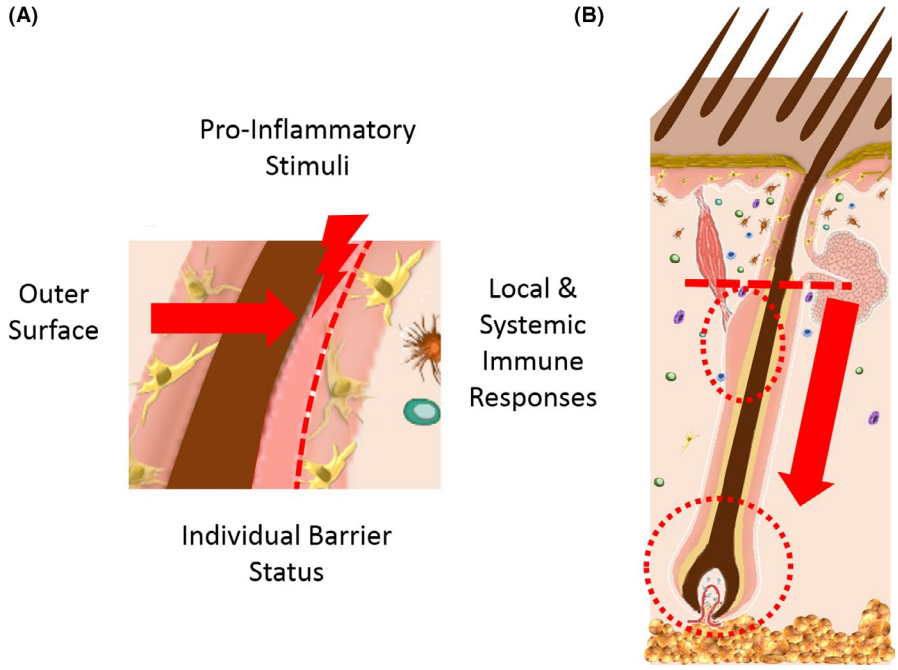


**FIGURE 2** Understanding how microbial colonization or deposition of contaminants on the surface of the hair follicle epithelium may interact with the barrier status under the influence of individual predisposition and additional local inflammatory stimuli, may help understand local flare-ups of inflammatory hair diseases (A). With respect to deeper compartments of the hair follicle, the penetration studies point towards a special vulnerability of the hair follicle during anagen phase, when hair growth crucially depends on a robust immune privilege around the bulb. With this respect, the question arises as to whether inappropriate deeper penetration of exogenous material or microbes, or dysbiosis as frequently observed in the context of associated atopic dermatitis, may contribute to destabilization of the immune privilege (B)

titanium dioxide particles as a possible trigger of chronic inflammation were generated. However, the results were limited by the small number of patients and the fact that similar deposits were also observed in negative controls,[71] illustrating the challenges associated with hair follicle research. Factors associated with shifts in microbial colonization have not been explored. Among a multitude of signalling pathways, AhR signalling in the epidermis studied in scalp skin affected by frontal fibrosing alopecia or lichen planopilaris[72] could be an interesting link, as it is a sensor for both, exogenous stimuli as well as endogenous ligands.[73] It may even point to host microbiome interactions as altered AhR signalling to microbiota typically found in hair follicles was recently reported for Malassezia species[74] and Staphylococcus epidermidis.[75]

With respect to deeper compartments of the hair follicles, the penetration studies point towards a special vulnerability of the hair follicle during anagen phase. At a time when hair growth crucially depends on a robust immune privilege around the bulb, the penetration rates are enhanced. With this respect, the question arises as to whether inappropriate deeper penetration of exogenous material or microbes, or dysbiosis as frequently observed in the context of associated atopic dermatitis, may contribute to the destabilization of the immune privilege (Figure 2B). At this point, we do not know how individual invasion factors of bacterial species or changes in the architecture of the root sheaths and associated tight junctions throughout the hair cycle may influence penetration depth, accessibility of viable cells and responsiveness of the tissue. It also remains unclear as to how particularities of the skin barrier of an individual, for example, filaggrin deficiency or alterations in lipid architecture, may modulate such processes. Interestingly enough, alopecia areata, a non-scarring alopecia characterized by deep peribulbar infiltrates, is frequently associated with atopic dermatitis. But a possible role of skin barrier deficiency as contributor to immune privilege instability in deeper hair follicle compartments has not been explored yet. Interestingly, microbiome alterations on and in scalp skin of alopecia areata patients compared to healthy individuals have been found in swab analyses and in skin biopsies, which were split into deep epidermis, dermis and hypodermis.[76]

## 4 | MAJOR OPEN RESEARCH QUESTIONS

Taken altogether, we oversee a large body of data obtained from skin barrier studies as well as allergological, toxicological, pharmaceutical and immunological investigations, all which point to the relevance of the hair follicle as an interface for cross-talk between components on the outside of the hair follicle epithelium and the underlying tissue. We understand that depending on the type of stimulus such interactions can trigger local inflammatory responses and or initiate systemic immune responses.

- But we poorly understand how such events may interfere with the maintenance of critical hair follicle structures, for example, the maintenance of the immune privilege in the bulge and the bulb area.
- We poorly understand the impact of external and local factors on flare-ups or recurrences of inflammatory hair diseases.
- Lastly, we only have very limited information on the typical content and on the penetration depth of exogenous compounds in a hair follicle infundibulum. Although it is known that microbial communities reside attached to epithelial surfaces along the hair follicle canal, we only partially understand to what extent shifts in their distribution and metabolic activity may impact physiological hair growth and cycling.

## 5 | CHALLENGES AND PERSPECTIVES

While the rationale for such investigations on the interplay between the barrier status, exogenous factors and individual responses are strong, it is extremely difficult to dissect these components in experimental studies. Data generated from material collected from patients are largely exploratory and frequently limited by small patient numbers.

Tissue culture models of diseases based on biopsies or hair follicle explants[77] face limitations with regard to time periods they can be kept in culture. Although recently proposed ex vivo explant models of human skin demonstrated the feasibility of culturing bacteria on excised human skin,[78] targeted colonization or introduction of exogenous compounds to the hair follicle surface for subsequent experimental studies is extremely difficult. As long as in vitro modelling of hair follicles remains a challenge, systematic interventions are typically limited to animal studies, ideally xenograft mouse models.[79] With this respect, 3D bio-printing technologies could become an interesting new strategy.[80] Incorporation of mutant cell populations, for example, could help decipher the relevance of barrier genes in analogy to experimental work in reconstructed skin models.[81]

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### CONFLICT OF INTEREST

The authors do not have further conflicts of interest in this field of research.

### AUTHOR CONTRIBUTION

AV and BC wrote the manuscript based on the experimental work conducted in the projects listed in the acknowledgement section, the co-authors added expertise in the following fields: AC: hair follicle microbiome, graphics, FR: drug delivery, KG: inflammation, IL-17, UBP: hair diseases, all authors read and approved the final manuscript.

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