A folliculocentric perspective of dandruff pathogenesis: Could a troublesome condition be caused by changes to a natural secretory mechanism?

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Abstract
Dandruff is a common scalp condition, which frequently causes psychological distress in those affected. Dandruff is considered to be caused by an interplay of several factors. However, the pathogenesis of dandruff remains under-investigated, especially with respect to the contribution of the hair follicle. As the hair follicle exhibits unique immune-modulatory properties, including the creation of an immunoinhibitory, immune-privileged milieu, we propose a novel hypothesis taking into account the role of the hair follicle. We hypothesize that the changes and imbalance of yeast and bacterial species, along with increasing proinflammatory sebum by-products, leads to the activation of immune response and inflammation. Hair follicle keratinocytes may then detect these changes in scalp microbiota resulting in the recruitment of leukocytes to the inflammation site. These changes in the scalp skin immune-microenvironment may impact hair follicle immune privilege status, which opens new avenues into exploring the role of the hair follicle in dandruff pathogenesis. Also see the video abstract here: https://youtu.be/mEZEznCYtNs

KEYWORDS
dandruff, hair follicle, immune privilege, inflammation, keratinocytes, seborrheic dermatitis

INTRODUCTION

Dandruff (pityriasis capitis, syn. pityriasis simplex capillitii) is a common, chronic scalp condition that affects more than half of the world’s population and has been known since antiquity.¹,² Beginning around or post-puberty,³⁴ dandruff can be a distressing condition, mainly due to its chronic nature, visible appearance and recurrence, resulting in psychosocial embarrassment for the individual.⁵⁶ The condition is limited to the scalp and is characterized by a combination of flaking, pruritus and mild inflammation, which can be associated with either oily (seborrheic) or dry scalp skin types.⁷⁸

Dandruff is considered to be on the same disease spectrum as seborrheic dermatitis (SD), which is a common, chronic inflammatory skin disorder that is not restricted to the scalp (affecting also the central face, anterior chest and body areas rich in sebaceous glands (SGs)), and is frequently more erythematous and inflamed.⁹ The differences between normal-, dandruff- and SD-affected scalp skin are illustrated in Figure 1A, B and C.
Even though it is one of the most frequent and universal dermatological problems, affecting billions of individuals worldwide regardless of gender and ethnicity[3] and has long fascinated leading dermatologists,[1] dandruff is relatively under-investigated compared with other skin disorders characterized by pityriasis. Nevertheless, the pathobiology of dandruff raises many intriguing questions at the core of human skin physiology and pathology, and is thus well-worth pondering in-depth.

Historically, many theories of the pathogenesis of dandruff have been proposed. Dandruff was considered a “sebaceous disease” during the 19th century due to the early observation of “fungus” Pityrosporum ovale (now named Malassezia) in dandruff scalp.[1,10] Today, the pathogenesis of dandruff is accepted to be multifactorial, but the key factors that drive its pathogenesis are less clear than the rapid response of dandruff to yeast-decimating anti-dandruff shampoos, creams and gels,[11] which has long been suggested. The factors that have been given the greatest amount of attention are: (a) (over-) colonization with yeast (Malassezia species),[12–14] (b) imbalance of bacterial species,[15–17] (c) disrupted epidermal barrier function,[8,18,19] (d) increased sebum-derived fatty acid metabolites and peroxidation of sebum component (squalene)[20,21] and (e) perivascular leukocyte infiltration, all of which may individually or jointly induce immune response and mild scalp skin inflammation.[18] These factors contribute to an increase in the proliferation of basal layer epidermal keratinocytes (KCs), which in turn results in a greater rate of corneocyte (retained with an intercellular adhesion called corneodesmosomes) production and shedding, manifesting clinically as dandruff.[8,18,22]

Given that this constellation shows major overlap with SD,[22] several authors regard dandruff as a relatively minor and less-inflammatory variant of SD (Table 1).[3,24] Yet, how to effectively distinguish between these entities remains a matter of debate. Dandruff displays some features typically associated with psoriasis such as parakeratosis and the presence of neutrophil-chemotactic anaphylatoxins in dandruff flakes (Table 1).[18,22,24,25] This strongly suggests that dandruff is less a specific disease entity than an epidermal response pattern[26] to a wide range of as yet insufficiently defined stimuli, clinically characterized by pityriasis, whose phenotypic manifestation likely is influenced by multiple constitutive factors including an individual’s genotype (23andMe Research, accessed on 1/10/2020), epidermal barrier function,[18,22] lipid metabolism,[20,21,27,28] skin microbiota,[8] poor scalp hygiene,[29] emotional stress[30] and possibly environmental factors such as humidity and seasonal changes.[31]

Although dandruff exclusively occurs on the scalp, surprisingly, previous dandruff studies have focused solely on dandruff scalp skin without systematically addressing the role of the hair follicle (HF), which deserves to be thoroughly investigated. Therefore, it is important to provide an up-to-date synthesis of our limited current understanding of dandruff pathobiology, which factors in a “folliculocentric” perspective on dandruff—namely by acknowledging the HF immune microenvironment and the status of HF immune privilege to permit a more comprehensive understanding of dandruff pathogenesis.
### TABLE 1

A detailed comparison of dandruff, seborrheic dermatitis and psoriasis

| Key features                        | Dandruff                          | Seborrheic dermatitis                  | Psoriasis                      | Reference |
|-------------------------------------|-----------------------------------|---------------------------------------|---------------------------------|-----------|
| **Location**                        | Scalp only                        | Areas rich in sebaceous glands such as the scalp, face, the upper chest and folds behind the ear | Elbows, scalp, knees, umbilicus, and lumbar region. Other less common areas are nails, palms and soles or face | [2,23] |
| **Prevalence**                      | 50%                               | 1%–3%                                 | 1%–3%                           | [6,32,33] |
| **Age groups affected**             | High amongst 15–24 year olds, decreasing with age | Peaking between the age of 2–12 months, then again in puberty and the third peak in adults 40–60 years of age | More common in adults than in children | [24,32,34] |
| **General clinical presentation**   | Scalp flaking, mild inflammation, and itchiness | Redness and itchiness of the affected area with erythematous plaques including yellow greasy scales | Red, circular, well-defined plaques with grey/ silver-white color dry scale | [4,32,33] |
| **Causes**                          | High abundance of Malassezia yeast, imbalance of bacterial species, epidermal barrier (EB) dysfunction, increased production of sebum-derived fatty acid metabolites, immune response by host and genetic predisposition | High abundance of Malassezia yeast, increased sebum production, EB dysfunction and other factors such as stress, hormones and weakened immune system | EB dysfunction, disruption of innate and adaptive immune responses, genetics and triggering factors such as infection, stress and trauma | [23,35,36] |
| **Histological and immunological features** | Parakeratosis, acanthosis and corneocyte membrane interdigitation. Presence of perivascular leukocyte in dandruff scalp and C5a in dandruff flakes | Parakeratosis, hyperplasia, spongiosis, plugged follicular ostia, superficial perivascular and perifollicular inflammatory infiltration | Parakeratosis, acanthosis with elongated rete ridges, thin granular cell layer and neovascularization. Infiltration of dermal dendritic cells, macrophages, T cells and neutrophils (present in parakeratotic scale) | [8,18,25,36,37] |

### A CLOSER LOOK INTO DANDRUFF ENVIRONMENT: BIOLOGY OF SCALP SKIN AND HAIR FOLLICLE

**The rich microbiota of scalp skin and hair follicles**

Scalp skin is unique in that it is highly innervated, abundantly vascularized, and has the highest density of terminal anagen VI HF s associated with SG s (Figure 2).

The vast majority of epithelial cells are HF KC s whose secretory activities reach down into dermal adipose tissue and dominate the overall signaling milieu of scalp skin.

These HF KC s play a role in itch sensation, a key symptom of inflammatory scalp skin disorders, by producing pruritogenic neuromediators such as β-endorphin and endovanilloids.

The HF creates a unique immune-microenvironment that is divided into a distal, fully immunocompetent compartment above the bulge and a profoundly immunoinhibitory, immune-privileged signaling milieu proximal to it (Figure 2A).

Below its “immunological watershed” above the bulge, the proximal portion of the HF exhibits immune privilege (IP), that is, an inhibitory tissue state generated by the combination of low or absent expression of MHC-class I/β2 microglobulin and MHC class II, along with the up-regulation of locally secreted immune-suppressants (details, see Figure 2A).

Within the HF infundibulum, the presence of sebum limits the types of microorganisms that can inhabit this ecological niche and the presence of commensal microorganisms forms an environment that discourages colonization by foreign pathogens (Figure 2B). In contrast to the epidermis and its stratum corneum (SC), the human HF epithelium represents a moist, much less acidic, relatively UV-protected, compact tissue column that creates an ideal habitat for microbial communities, which gain access to deeper skin layers and impact on the secretory activity of HF KC s, such as the release of chemokines and antimicrobial peptides (AMPs) such as psoriasin and RNase 7. Though this awaits systematic characterization in dandruff scalp skin, it must be assumed that any kind of dysbiosis of the human HF microbiota results in significant alterations of this secretory activity.
### TABLE 2  The function and localization/ expression of key immune privilege markers

| Key immune privilege markers | Function | Expression/ Localization | References |
|-----------------------------|----------|--------------------------|------------|
| α-MSH                       | Neuropeptide with functions in regulating immune and pigmentary homeostasis. Functions as an anti-inflammatory agent that maintains immune privilege | Expressed on keratinocytes in the outer root sheath (ORS) and epidermis | [56,60] |
| β2-microglobulin            | Part of the heterodimer structure of both MHC class I molecules. Stabilizes the structure of MHC class I molecules | Expressed on keratinocytes in distal ORS and epidermis | [54,61,62] |
| CD200                       | A potent immunosuppressive protein considered an IP marker. Provides a “no danger” signal to the immune system protecting the bulge from autoimmune destruction | Expressed on epithelial stem cells in the bulge | [56,63,64] |
| Cortisol                    | A stress hormone with effect on the function of hair follicle and regulation of the hair cycle | Secreted by the hair follicle | [45,66] |
| IGF-1                       | An immunosuppressive hormone with a molecular structure resembling insulin | Widely expressed in the hair follicle including the hair bulb | [56,64] |
| IL-10                       | A potent cytokine with anti-inflammatory activity. Influences immune responses | Generated by keratinocytes in the proximal hair follicle | [67,68] |
| MHC class I                 | Presents peptide to CD8+ cytotoxic T cells, which leads to the initiation of immune response | Expressed on keratinocytes in the distal ORS and scalp epidermis | [54,61,69] |
| MHC class II                | Presents peptide to CD4+ T helper cells | Expressed on the surface of professional antigen cells such as dendritic cells (DCs) and macrophages. Expressed on keratinocytes from distal to proximal ORS and epidermis | [62,70,71] |
| TAPs                        | Involved in the loading of (self-) peptide onto MHC class I | Expressed on keratinocytes in the distal ORS with lower expression in the proximal ORS, hair matrix and dermal papilla | [61,72] |
| TGFβ1/2                     | Functions as an immunosuppressant within the hair follicle | Expressed on keratinocytes in the ORS | [61,73] |

Promotes immune tolerance, inhibits inflammation and restricts antigen presentation, and is thus a preferred habitat for diverse microbiota, notably including viruses, that evade immune elimination.[45,54–56] Moreover, the vast majority of HFs in non-alopecic scalp skin are in anagen.[57] Extrapolating from mouse skin, where all HFs are in anagen phase and shows a profound, but physiological state of immunosuppression,[55,58] it is likely that healthy scalp skin, overall, is also relatively immunoinhibited. While this remains to be investigated, it is eminently conceivable that HF IP dysbiosis can lead to the increased secretion of AMPs, chemokines and cytokines by a large population of scalp HFs, resulting in a switch in their milieu into a pro-inflammatory one, to which basal layer epidermal KCs may then respond with increased proliferation.[22]

**THE CAUSES OF DANDRUFF ARE OFTEN MULTIFACTORIAL AND INTERLINKED**

**Higher abundance of yeast present in dandruff scalp**

*Malassezia* spp. are lipophilic yeast organisms commonly found in healthy human skin including the scalp, especially in the HF infundibulum.[74] The abundance of *Malassezia* spp. is increased and often associates with the HF in dandruff-affected scalp skin,[24] similar to what is seen in SD and atopic dermatitis (AD), both of which are characterized by a defective skin barrier and immune dysregulation.[23,75,76] On dandruff-affected scalp, *M. restricta* is present at a higher abundance alongside, but to a lesser extent, *M. globosa* and *M. furfur*.[13,17,48,77] There is also a high abundance of unclassified *Malassezia* spp. in dandruff scalp.[17,48,78] *Malassezia* spp. depend on the host’s sebum lipids as their main nutrient source, as they lack the enzyme fatty acid synthase to synthesize fatty acids (FAs).[79] *Malassezia* spp. hydrolyze the host’s sebum,[12,79–81] leading to the release of unsaturated FAs such as oleic acid and arachidonic acid as by-products.[80] These pro-inflammatory unsaturated FAs penetrate through the epidermal barrier, leading to epidermal hyperproliferation.[82] In vivo, oleic acid indeed disrupts the skin barrier and causes skin irritation.[83] In another study, scalp application of 7.5% oleic acid caused pityriasis only in dandruff-susceptible individuals, which was ultra-structurally indistinguishable from spontaneous dandruff flakes.[84] In differentiated human epidermal KCs in vitro, both (unsaturated) oleic acid and (saturated) palmitic acid were reported to increase IL-1α production.[85] Therefore, excessive exposure of scalp epidermis to both types of FAs could play a role in dandruff pathogenesis. Mechanistically, however, it remains unclear.
whether and how exactly *Malassezia* spp. and the FAs released by them initiate the pathobiology events leading to dandruff and skin irritation or whether they become involved at some other point during the pathogenesis course.

**Sebum production and its peroxidised by-product**

Sebum is produced and released by sebocytes in the SG via the sebaceous duct to the HF canal and the skin surface.[86] Sebum lipids consist of a mixture of triglycerides, wax esters, free fatty acids, cholesterol and squalene that is consumed by commensal microorganism such as *Malassezia* spp. In dandruff scalp, squalene is significantly peroxidised resulting in a higher level of squalene mono-hydroperoxide (SQOOH).[20] This is important as in vitro studies have shown that *Malassezia* induces squalene peroxidation,[27] and that SQOOH can stimulate KC proliferation and inflammatory responses, which could possibly damage the scalp epidermal barrier.[28] Yet, the specific role of SQOOH in dandruff pathobiology requires further investigation.

It is also as yet unclear how the amount of sebum production, which mainly reflects the degree of sebocyte proliferation,[87] and the development of dandruff are linked (notably, some SD patients have normal sebum production, while individuals with excessive sebum production do not necessarily develop SD[88]). Nevertheless, experimental reduction of lipid synthesis in sebocytes reportedly protects the epidermis from *Malassezia*-induced morphological changes, while both dandruff and scalp sebum production were significantly reduced in a clinical study using 1.5% *Epilobium angustifolium* extract.[21]

**Could bacterial species have greater contribution than yeast in the dandruff pathogenesis?**

Besides yeasts, bacterial species have also been implicated in dandruff pathogenesis.[12,15,16] *Cutibacterium* and *Staphylococcus* are the most
dominant commensal bacteria on the scalp. Several studies have reported a higher abundance of S. epidermidis and reduced abundance of C. acnes in dandruff subjects, and the S. epidermidis and C. acnes profile may be more strongly associated with dandruff severity than that of Malassezia spp.

The specific interactions between Malassezia, Staphylococcus and Cutibacterium are not well understood. However, lessons can be learnt from in vitro and skin models to infer how certain microbes may gain an advantage to increase their abundance. For example, M. globosa secretes aspartyl protease (MgSAP1) which can reduce biofilm formation by S. aureus. Similarly, S. epidermidis produces Esp, a serine protease which limits colonization of S. aureus. The possibility also exists for C. acnes to inhibit S. aureus since this has been shown to occur in wounds due to fermentation of glycerol by C. acnes to short chain fatty acids (SCFA). However, the growth of C. acnes could also be limited by the same mechanism because S. epidermidis is also known to ferment glycerol to SCFA which inhibit Cutibacterium.

Both S.epidermidis and C. acnes can produce bacteriocins, which induce peptide-mediated killing of bacteria closely related to the producer.

Together these described mechanisms could allow commensal scalp skin microbes to gain an advantage over one another within dandruff scalp, however this remains to be investigated. This also further suggests that a dysbiosis of scalp skin bacterial species can contribute to dandruff pathogenesis. Potentially, overgrowth of Malassezia spp. may be a secondary response to primary bacterial dysbiosis, which would imply that re-balancing of these microbial communities or targetting the release of certain proteins that enable bacterial species to gain advantage in the ecological niche is a key therapeutic challenge within dandruff management.

Distinctive changes in morphology, lipid content, and imbalance of protease inhibitor and protease level within the epidermis

Given that roughly half of the global population experience dandruff, individual susceptibility factors must play a critical role in whether the dandruff pathogenesis elements discussed above result in clinically visible dandruff formation. Genetic susceptibility could possibly play an important role in determining an individual's propensity to develop dandruff, as a preliminary report has identified 487 genetic markers that are presumably associated with dandruff (23andMe Research, accessed on 1/10/2020). While genetic studies have revealed a constitutive predisposition to epidermal barrier dysfunction in SD patients, similar studies in dandruff patients require a thorough investigation.

The epidermis of dandruff scalp displays significant morphological changes such as an altered SC ultrastructure, more convoluted dermal-epidermal junction, deeper rete ridges and a lack of desmosomes within the epidermis. The normal epidermal thickness and basket weave structure of the SC (Figure 3A and B) is visibly altered in dandruff scalp skin: irregular epidermal hyperplasia (acanthosis) occurs as a result of increased epidermal KC proliferation that mounds in abnormal epidermal terminal differentiation along with parakeratosis (Figure 3C) that is, the retention of nuclei within corneocytes. In dandruff lesions, the epidermal thickness is increased by 66%, possibly explained by an increased percentage of proliferating Ki-67+ epidermal KCs. Histologically, the parakeratotic cells are surrounded by Malassezia yeast. Dandruff-associated parakeratosis typically exhibits a peri-infundibular "shoulder like" distribution and may be associated with follicular plugging, a stereotypic inflammatory response pattern of the distal HF epithelium leading to an increased keratin accumulation in the follicular ostium. The hyperkeratosis and parakeratosis correspond to excessive epidermal corneocyte shedding, which manifests clinically as pityriasis.

Besides a constitutively higher basal epidermal proliferation rate as a potential susceptibility factor, dry scalp is another hallmark of dandruff. This is reflected by a significant decrease in ceramides, FAs, cholesterol, sphingolipid precursors and barrier integrity proteins (keratin 1, -10, and -11) as well as by a decrease in the expression of genes involved in lipid metabolism. Furthermore, the level of human serum albumin, as a barrier integrity biomarker, and transepidermal water loss are both significantly increased in dandruff-lesions, suggesting reduced hydration across and within the SC. As these lipids and proteins form an integral component of the epidermal barrier, these findings suggest that there is a weakened epidermal barrier in dandruff scalp.

The SC of dandruff scalp also exhibits a raised level of serine protease inhibitors (LEKT1 and SCCA1) leading to an imbalance between inhibitor and protease levels. This leads to an abnormal desquamation process where the surface of corneocytes still retain corneodesmosomes in dandruff scalp. In mice, the deletion of serine protease Kallikrein-related peptidase 5 (Klk5) along with application of oleic acid leads to development of dandruff-like symptoms such as flaking, hyperkeratosis, acanthosis and inflammation.

However it is as yet quite unclear whether the epidermal and/or follicular changes described above precede the inflammatory changes occurring within the dermis, or vice versa, and the answer to this question is critical to elucidate the choreography of pathobiology events in dandruff. Therefore, it remains a challenge for future dandruff research to determine the exact sequence.

Inflammation and the presence of perivascular leukocytes in dandruff scalp

The host's immune response is another key susceptibility factor to be considered in dandruff pathogenesis, since there is the infiltration of perifollicular and perivascular leukocytes in dandruff tissue (Figure 3C). This is indicative of mild inflammation, as these leukocytes only migrate from the bloodstream to a site of injury or infection after endothelial cell activation, thereby promoting skin inflammation. This raises a key question: how does the dermal vasculature become activated in dandruff in order to attract an inflammatory infiltrate?
Besides the mechanisms mentioned above, we do know that there is a significant increase in epidermal inflammation markers, for example, of the neutrophil chemoattractant IL-8\(^{25,107}\) and of IL-1\(\alpha\) and IL-1RA in dandruff-affected scalp\(^{8,18}\). Furthermore, dandruff scales reportedly contain neutrophil-chemotactic anaphylatoxins, which suggests that classical complement pathway activation with increased C5a production is involved in neutrophil migration into dandruff-affected epidermis\(^{25,108}\). However, in Leiner’s Disease, the congenital deficiency in complement component 5 (OMIM#609536) causes extensive SD\(^{109,110}\). The exact reason for this difference in dandruff versus SD is unknown; however, it could possibly be used to differentiate between the two similar but different conditions. In psoriasis, activated neutrophils release neutrophil extracellular traps (NETs) during NETosis which contribute to skin inflammation via the...
activation of inflammasome and of TLR4/IL-36 crosstalk in skin. It is tempting to speculate that this mechanism could aggravate inflammation during the later stages of dandruff pathogenesis.

Is the innate immune system and hair follicle responding to the changes in dandruff scalp microbiota?

As the innate immune system is prominently activated by and responds to the presence of Malassezia spp, as observed in KCs, we can speculate that similar mechanisms occur in both epidermal and HF KCs in dandruff scalp. M. furfur upregulates the expression of TLRs (in particular TLR2, which is also expressed in HF), IL-8 and AMPs such as human β-defensins in KCs. M. furfur also activates the NLRP3 inflammasome, a multi-protein oligomer present in the cytoplasm of KCs that plays a key role in activating inflammatory responses leading to the secretion of the pro-inflammatory cytokine IL-1β in human antigen-presenting cells via Syk-kinase signaling. This is important, as the NLRP3 inflammasome has been shown to be activated via TLR3 in the HF outer root sheath when triggered by dsRNA, which leads to the secretion of IL-1β and HMGB1. Interestingly, IL-1β staining has been reported to be increased in lesional versus non-lesional skin in SD. Together this suggests that the NLRP3 inflammasome could promote the release of pro-inflammatory cytokines to promote dandruff pathogenesis; however this speculation requires further investigation.

In addition, immune cells can sense microbes through intact barriers, and modulate skin microbiota by regulating sebum production. In a mice study, innate lymphoid cells residing within the HF were shown to modulate sebum secretion and antimicrobial lipid production, and subsequently the commensal bacterial communities on the skin. Given the overall impact of HFs on scalp skin immune status and immune responses (see above), the constitutive activation status of immunocyte populations that link innate and adaptive immunity are highly responsive to dysbiosis. They (i.e., mast cells and macrophages) also densely populate the mesenchyme of human scalp HFs even under physiological circumstances. These immune cells may also modulate the strength and character of immune responses against changes in the skin's yeast and bacterial colonization. Therefore, it would be pertinent to determine whether the number of these specific immune cells increase around HFs in dandruff-scap.

INCORPORATING THE HAIR FOLLICLE INTO A MODEL OF DANDRUFF PATHOGENESIS

A folliculocentric perspective: How do scalp hair follicles impact dandruff pathobiology?

When viewed in isolation, the recognized elements of dandruff pathogenesis do not yet convincingly explain why dandruff is essentially a scalp skin phenomenon and how scalp HFs may impact upon it. Therefore, we delineate a hypothetical scenario that introduces a folliculocentric perspective into the dandruff pathobiology debate. Alongside with the normal scalp (Figure 4A), we have added a "priming" stage (Figure 4B) that represents non-lesional and peri-lesional skin of dandruff scalp as non-lesional dandruff scalp skin already shows microbial dysbiosis. Furthermore, Mills et al report via Gene Ontology analysis that non-lesional dandruff skin was enriched for "immune response" compared to healthy skin, arguing that this is a predisposing factor to dandruff development. As a result, this further highlights non-lesional skin may be "primed" to develop dandruff. Interestingly, this priming is also apparent in AD, whereby non-lesional and peri-lesional skin show barrier defects, an abnormal immune phenotype and Staphylococcus aureus colonization. Whilst it is unclear what comes first, it is plausible that this priming provides the perfect conditions to facilitate dysbiosis in dandruff (Figure 4C), which could also be in a manner akin to the gut, whereby gut inflammation and stress can lead to dysbiosis.

Our working hypothesis (Figure 4C) illustrates that the disruption of the epidermal barrier leads to over-colonization of Malassezia spp, both in the epidermis and within the HF infundibulum. This disrupts the balance of bacterial species resulting in increased S. epidermidis and decreased C. acnes. As a result, unsaturated FAs such as oleic acid generated from the hydrolysis of sebum by Malassezia spp, S. epidermidis and C. acnes are able to penetrate the weakened epidermal barrier, causing inflammation and initiating an immune response and subsequently exacerbates epidermal KC differentiation and barrier defects. HF KCs themselves may detect over-colonization/dysbiosis and thereby activate the immune system by recruiting immune cells and triggering the release of pro-inflammatory cytokines and chemokines, and AMPs. Cell surface antigens belonging to Malassezia or S. epidermidis may also play a part in activating the immunological auto-catalytic cascade to disrupt homeostasis.

We speculate that this coincides with a downregulation of immunoinhibitory HF IP guardians such as α-MSH, TGFβ1/2, IGF-1, cortisol and IL-10 that healthy human scalp HF KCs normally produce in abundance, thus further compromising the physiological immunoinhibitory milieu of scalp skin and accentuating the pro-inflammatory events depicted in Figure 4C. This, in turn, would up-regulate epidermal proliferation and promote abnormal KC differentiation, a greater rate of corneocyte production and ultimately resulting in pityriasis.

In this novel pathobiology scenario, the restoration of immunoinhibitory HF signals constitutes a key therapeutic target for a longer-lasting anti-dandruff effects than those that are currently achievable with standard anti-dandruff shampoos, which invariably fail to suppress dandruff recurrence after discontinuation. Another critical target for therapeutic intervention in this scenario is the restoration of the epidermal and infundibular barrier, whose disruption may initiate the dandruff pathobiology cascade (Figure 4C). Obviously, this leads us back to the question of what exactly provokes this barrier disruption. One contribution might be skin and/or HF dysbiosis (see above) as well as the balance between over and under-shampooing.
FIGURE 4  Dandruff pathobiology: A folliculocentric working model. (A) Shows the presence and distribution of yeast and bacterial species, and immunocytes in normal healthy scalp. (B) Illustrates the "priming" stage where the non-lesional and peri-lesional dandruff scalp is primed for the development of dandruff lesional scalp (*). The existence of inflammatory milieu (1)[8] and epidermal changes/epidermal barrier dysfunction (2)[22] could lead to dysbiosis occurring within the "priming" stage leading to dandruff lesional scalp. (C) We hypothesize that a weak epidermal and/or infundibular skin barrier (1) disrupts the balance between yeast and bacterial species in scalp skin and HF, with over-colonization of Malassezia spp., higher abundance of S. epidermidis and reduced C. acnes abundance (2). Proinflammatory sebum-derived fatty acid metabolites such as oleic acid can then penetrate the (either constitutively weak or exogenously compromised) epidermal barrier (3), leading to the activation of the immune response causing inflammation (4). In dandruff epidermis, there is an increase in IL-8 (5)[8,18] Over-colonization with Malassezia
POSSIBLE TARGET FOR DANDRUFF THERAPY

An effective treatment for dandruff is zinc pyrithione (ZPT) which inhibits M. restricta in dandruff via three different inhibitory mechanisms, that is, by increasing zinc levels inside yeast cells, promoting mitochondrial dysfunction and reducing lipase expression. However as ZTP is a pleiotropic drug, it may exert effects on the epidermis that go beyond this anti-fungal effect. Indeed, other effective anti-dandruff therapies can also exert direct effects on the epidermis which might contribute towards the resolution of symptoms. Specifically, selenium sulphide, ketoconazole, coal tar, piroctone olamine and corticosteroids are also pleiotropic drugs that affect host tissues.

ZPT is a zinc ionophore which helps to transport the zinc ion across the lipid cell membrane leading to an increased intracellular concentration of zinc. ZPT has recently been shown to increase the intracellular concentration of zinc in mammalian cells and tissue. Zinc is also an important regulator of epidermal homeostasis as it is involved in numerous enzymatic reactions and transcriptional activities, and is known to regulate the barrier via modulation of tight junctions. In addition, Zinc ion is anti-inflammatory and antimitic, and water-soluble ZPT analogs inhibit cell proliferation and promote apoptosis. Furthermore, in SD patients, serum zinc levels are lower in comparison to healthy patients. Zinc deficiency has been reported to induce membrane barrier dysfunction, increase secretion of IL-8 and promote neutrophil migration in vitro. While there is lack of research on zinc levels in dandruff patients, overall we can speculate that zinc deficiency might contribute to dandruff pathogenesis, and warrants further investigation.

In addition, ZPT is delivered at an approximate 10–20 μm depth of the sebum-rich infundibulum, this illustrates the importance of the hair follicle in dandruff treatment. Considering all of this, future anti-dandruff treatments should strongly also take the role of hair follicle into consideration as well as its’ wide range of secretory proteins and cytokines potentially involved in an inflamed dandruff milieu as a potential target for anti-dandruff therapy.

Until this is accomplished, dandruff sufferers and their physicians may wish to contemplate one final thought: One tends to forget that enhanced corneocyte production and shedding—just like its sister phenomenon hair shaft shedding, as unwelcome as both may be psychosocially—is a very effective “holocrine” excretory mechanism for eliminating noxious agents by embedding them into (and thus neutralizing them within) cells that are subsequently shed into the environment. Therefore, one wonders whether dandruff may even fulfill excretory functions in eliminating potential noxi from the human organism. If so, it may be wisest to only reduce/minimize, however not completely abrogate dandruff.

CONCLUSIONS AND OUTLOOK

Dandruff is a common, mildly inflammatory scalp health disorder whose pathobiology remains insufficiently understood. However, we have singled out (1) dysbiosis (Malassezia spp. over-colonization and an imbalance of commensal bacterial species such as S. epidermidis and C. acnes), (2) constitutive or acquired epidermal/infundibular barrier disruption, (3) host’s immune response, and (4) an insufficient immunoinhibitory signaling milieu, normally generated by terminal anagen scalp HFs, as key elements in dandruff pathogenesis.

To shift its current predominant focus on Malassezia over-colonization to an underestimated central actor in the dandruff theatre, that is, anagen scalp HFs, we propose a new, provocatively folliculocentric working hypothesis of dandruff pathogenesis. If confirmed, therapeutically, this pathobiology scenario requires a stringent focus on the long-lasting re-establishment of HF IP and the HF-dependent immunoinhibitory physiological signaling milieu of healthy scalp skin.

None of the therapeutic actives in anti-dandruff shampoos penetrates deep enough into the central and lower HF epithelium to greatly affect (a) the entire HF microbiota and/or (b) the HF immune system, nor are they (c) recognized to improve barrier function. There is a lack of hard evidence that they impact on d) the delicate balance between proinflammatory chemokines, cytokines, AMPs and immunoinhibitory IP guardians that scalp HFs produce and secrete, whose imbalance may be a key driving force in dandruff pathogenesis. Translationally, one logical consequence of our folliculocentric scenario is to re-focus future research efforts on the development of well-tolerated...
cosmeceuticals that impact on/execute (a)–(d). Along with available standard anti-dandruff shampoos, creams and gels, such novel, HF-targeting anti-pityriasis agents promise to open a new chapter in gaining mastery over dandruff.

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CONFLICT OF INTEREST
While the authors perceive no conflict of interest, for the record, R.P. is founder & CEO of Monasterium Laboratory Skin & Hair Research Solutions, a company engaged in skin and hair research, while R.K.B. is an employee of a company that markets personal care products.

AUTHOR CONTRIBUTION
Susan L. Limbu wrote the manuscript. Talveen S. Purba, Matthew Harrries, Tongyu C. Wikramanayake, Mariya Miteva, Ranjit K. Bhogal and Catherine A. O’neill all provided extensive scientific and writing contribution. Mariya Miteva provided the clinical and histology images, and Ralf Paus conceived, contributed extensive scientific knowledge and edited the manuscript.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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