Frontiers in Lichen Planopilaris and Frontal Fibrosing Alopecia Research: Pathobiology Progress and Translational Horizons

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Lichen planopilaris (LPP) and frontal fibrosing alopecia (FFA) are primary, lymphocytic cicatricial hair loss disorders. These model epithelial stem cell (SC) diseases are thought to result from a $CD8^+$ T-cell–dominated immune attack on the hair follicle (HF) SC niche (bulge) after the latter has lost its immune privilege (IP) for as yet unknown reasons. This induces both apoptosis and pathological epithelial–mesenchymal transition in epithelial SCs, thus depletes the bulge, causes fibrosis, and ultimately abrogates the HFs' capacity to regenerate. In this paper, we synthesize recent progress in LPP and FFA pathobiology research, integrate our limited current understanding of the roles that genetic, hormonal, environmental, and other factors may play, and define major open questions. We propose that LPP and FFA share a common initial pathobiology, which then bifurcates into two distinct clinical phenotypes, with macrophages possibly playing a key role in phenotype determination. As particularly promising translational research avenues toward direly needed progress in the management of these disfiguring, deeply distressful cicatricial alopecia variants, we advocate to focus on the development of bulge IP and epithelial SC protectants such as, for example, topically effective, HF–penetrating and immunoinhibitory preparations that contain tacrolimus, peroxisome proliferator–activated receptor-γ, and/or CB1 agonists.

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Abbreviations: 5ARI, 5α-reductase inhibitor; α-MSH, α-melanocyte-stimulating hormone; AA, alopecia areata; AGA, androgenetic alopecia; CRH, corticotropin-releasing hormone; eHFSC, epithelial hair follicle stem cell; EMT, epithelial–mesenchymal transition; FFA, frontal fibrosing alopecia; HF, hair follicle; IP, immune privilege; K, keratin; KC, keratinocyte; LPP, lichen planopilaris; MAC, macrophage; MHC, major histocompatibility complex; PCA, primary cicatricial alopecia; PCP, personal care product; PPAR-γ, peroxisome proliferator–activated receptor-γ; SC, stem cell; SP, substance P

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THE CHALLENGE

Lichen planopilaris (LPP) and frontal fibrosing alopecia (FFA) are inflammatory scarring hair loss disorders that primarily affect perimenopausal and postmenopausal women. These primary cicatricial alopecias (PCAs) result in disfiguring hair loss, significant scalp symptoms, secondary cutaneous morbidity, (Fertig et al., 2018), severely reduced QOL, and significant psychosocial burden (Chiang et al., 2015). Yet, rarely can dermatologists provide these patients with rapid, robust, and meaningful therapeutic interventions today.

Unfortunately, the evidence-based foundation on which to build treatment guidelines and predict outcomes remains painfully thin, despite laudable attempts by many investigators (for recent examples, see Dadkhahfar et al. [2020], Fatemi Naeini et al. [2020], Fertig and Tosti [2016], Peterson et al. [2019], Preda-Naumescu et al. [2021], Vañó-Galván et al. [2021], and Villani et al. [2021]). Thus, there is an enormous need to improve the field's understanding of these irreversible and traumatizing alopecias, for which many key parameters remain unclear: the exact prevalence as well as the demographic and ethnic distribution within defined populations; reliable and predictive biomarkers of disease activity, course, and therapeutic response; and genetic, environmental, microbial, cosmetic, and nutritional factors at play in both populations and individuals, which are (i) shared between and (ii) distinct to LPP/FFA.

Our best bet for overcoming these frustrating limitations arguably is to refocus attention on the underlying shared and distinct pathobiology mechanisms in LPP versus FFA—because this carries the highest likelihood of leading to targeted and effective therapeutic interventions at a justifiable risk-benefit ratio while facilitating management strategies tailored to a given patient's specific pathobiology constellation and biomarker expression profile. Guided by this overarching goal and the authors' personal clinical and basic research experience in this field, the current review synthesizes recent progress in LPP and FFA pathobiology research and suggests concrete avenues toward the development of more effective therapeutics.

CONCEPTUAL PATHOBIOLOGY CONSIDERATIONS

Let us consider the major distinctive and shared features of LPP and FFA at the level of clinical presentation (Table 1 and Figure 1a and b) and (immuno-)histopathology (Table 1 and Figure 2a and b). These tables and figures show the histopathological similarity of both PCAs in striking contrast to their very distinct clinical phenotypes (although overlap variants do exist [Du et al., 2020; Griggs et al., 2021;

Table 1. Clinical and Immunohistopathological Characteristics of FFA and LPP

Diagnosis	Distinct Histopathological Characteristics[1]	Shared Histopathological Characteristics	Distinct Clinical Characteristics	Shared Clinical Characteristics
LPP	More severe inflammatory infiltrate and less apoptosis (Problet et al., 2006; Gálvez-Canseco et al., 2018) Concentric lamellar fibroplasia (Gálvez-Canseco et al., 2018) More basilar layer and interfollicular epidermal damage (Problet et al., 2006) Increased melanocyte counts in the upper hair follicle (Katoulis et al., 2020) DIF shows less IgM immunofluorescence and IgG, IgA, and IgM in papillary dermis (Cerqueira et al., 2016) Increased $CD68^+$ macrophage polarization and upregulated CD163 and IL-4 (Harries et al., 2020)	Lichenoid perifollicular lymphocytic infiltration (most evident in the superior aspects of the hair follicle) (Kurzeja et al., 2021; Stefanato, 2010) Infundibular hyperkeratosis and hypergranulosis. Hair epithelium shows vacuolar degeneration, necrotic keratinocytes, and perifollicular loss of elastin fibers with fibrosis (Ma et al., 2017) Superficial pigment incontinence (Wilk et al., 2013; Bolduc et al., 2016) Follicular plugging, epidermal/dermal clefts, and sebaceous gland destruction (Kang et al., 2008) The chronic stage shows dilated blood vessels and band-like vertical scarring beneath the papillary dermis (Kang et al., 2008) The late stage shows extensive perifollicular lamellar fibrosis surrounding the infundibulum (Kang et al., 2008) Similar expression profiles of CD1a, CD3, CD4, CD8, CD68, and IDO in immunohistochemical studies (Cerqueira et al., 2016) Increased $CD8^+$, $CXCR3^+$, $FOXP3^+$ T cells, and $CD68^+$ macrophages (Harries et al., 2020) Increased total and degranulated mast cells and $CD123^+$ dendritic cells (Harries et al., 2020) Decreased numbers of $CD1a^+$ and $CD209^+$ dendritic cells in the infundibulum connective tissue sheath (Harries et al., 2020)	Asymmetric multifocal involvement of scarring alopecia (Bolduc et al., 2016) Perifollicular erythema and keratotic follicular papules (Bolduc et al., 2016) Most commonly vertex and parietal scalp, but all regions can be involved (Stefanato, 2010) Association with oral, ungueal, or cutaneous lichen planus (Bolduc et al., 2016) Dermoscopy shows elongated concentric blood vessels, violaceous-blue interfollicular areas, and big irregular white dots (Bolduc et al., 2016)	Dermoscopy shows loss of follicular ostia, peripilar white scales, and peripilar erythema (Bolduc et al., 2016) Symptoms of pruritus, pain, and burning (Vañó-Galván et al., 2014)
FFA	Extension of the inflammatory infiltrate below the isthmus (Wong and Goldberg, 2017) Islands of sparing of interfollicular epidermis (Harries et al., 2013) Less prominent inflammatory infiltrate, with more numerous necrotic keratinocytes and foreign body reaction (Problet et al., 2006) More frequent terminal catagen–telogen hairs (Gálvez-Canseco et al., 2018) DIF shows cytoid bodies of IgM in the papillary dermis and epidermal and follicular basement membrane zones (Cerqueira et al., 2016) Increased Langerhans cells in the infundibuloisthmic region compared with that in LPP (Ma et al., 2017)		Symmetric, progressive frontotemporal hairline recession in a band-like pattern above the patient's normally pigmented and wrinkled forehead. Less frequent recession of preauricular and postauricular areas and occipital scalp. Dermoscopy shows peripilar white scales and erythema, regularly distributed red or gray dots in eyebrows, and peripilar erythema (Bolduc et al., 2016) Skin-colored facial papules. Marked or complete loss of eyebrows, typically beginning laterally (Bolduc et al., 2016) General thinning of the beard and peripheral body hair. Absence of vellus hair in the hairline.	

Abbreviations: DIF, direct immunofluoresence; FFA, frontal fibrosing alopecia; LPP, lichen planopilaris.
[1]Although several studies have found histopathological differences between LPP and FFA, all concluded that the findings are too subtle to distinguish the entities without clinical correlation.

Rigopoulos et al., 2015; Vañó-Galván et al., 2019a]). Thus, one key—as yet unanswered—question is how can two histologically deceptively similar diseases be clinically so distinct? Any plausible LPP and FFA pathobiology hypothesis must convincingly explain how such microscopic similarities can yield such distinct clinical features. Next, it helps to reflect the fundamental nature of both PCAs.

Regional versus systemic diseases

Specifically, we need to ask whether LPP and FFA are primarily regional (territorial) diseases dominated by localized epithelial hair follicle (HF) stem cell (eHFSC) pathology in defined, predilected skin regions, as we have argued before (Harries et al., 2018), irrespective of whether systemic and genetic elements may substantially modify disease phenotype, triggering, course, and response to therapy, or whether, vice versa, these PCAs are essentially systemic, genetically driven disease entities, where intracutaneous pathobiology elements and/or environmental factors merely modify the location, phenotype, and progression of individual LPP or FFA lesions but not the development and course of the disease as such, a view favored by some investigators (Tziotzios et al., 2019).

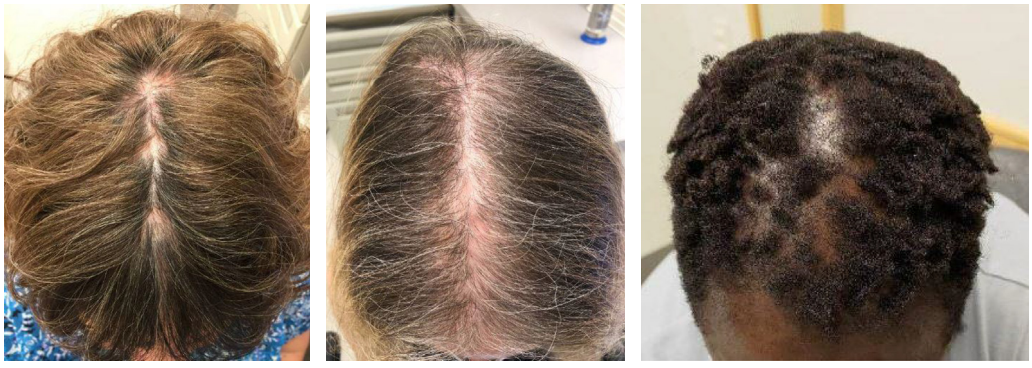
These conflicting concepts are by no means of mere academic interest because the former implies that optimal disease management primarily demands early and decisive intervention at the local skin level, whereas the latter suggests that systemic therapy will likely be much more effective and is thus more important than anything else if one wishes to halt the progression of these disfiguring hair diseases as soon as possible. Currently, arguments can be invoked that support either view or much further research is needed until it will become clearer which concept is best supported by evidence.

On the basis of recent studies and as depicted in Figure 3a, intracutaneous pathobiology elements and locally active environmental factors seem to be the key factors in the development of both LPP and FFA (Chiang et al., 2015, 2012; Harries et al., 2020, 2018). Such environmental factors may

a Biopsy-proven FFA

Fronto-temporal recession with band-like atrophic skin, loss of eyebrows, facial papules, perifollicular erythema, and lonely hairs.

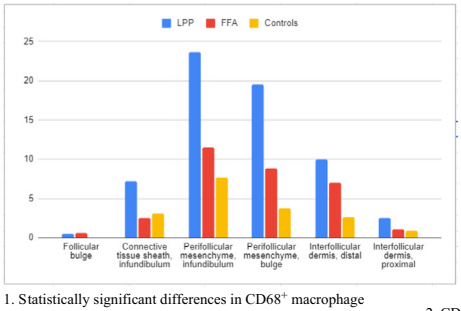
b Biopsy-proven LPP



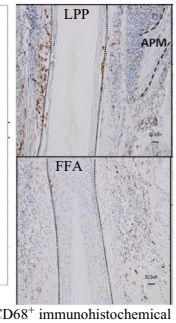
Asymmetric, multifocal, alopecia of vertex and parietal scalp. Perifollicular erythema and keratotic follicular papules.

Figure 1. Clinical characteristics of LPP and FFA. Macroscopic and dermatoscopic views of biopsy-proven (**a**) FFA and **(b)** LPP, showing the key clinical characteristics features. All subjects consented to the publication of the images. FFA, frontal fibrosing alopecia; LPP, lichen planopilaris.

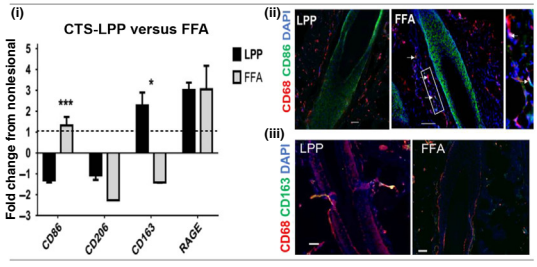
a Distinct features



1. Statistically significant differences in CD68$^+$ macrophage expression in patients with LPP, FFA and controls.

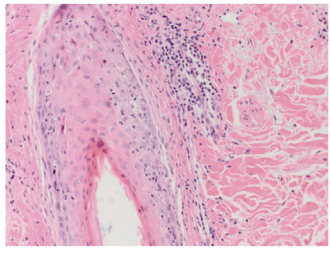


2. CD68$^+$ immunohistochemical markers at the hair follicle bulge region.

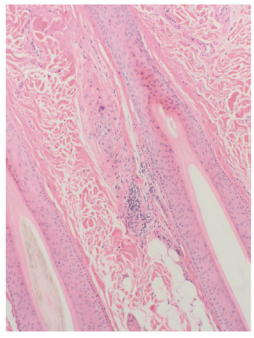


3. Downregulation of macrophage M1 marker CD86 versus M2 marker CD163 upregulation in LPP versus FFA.

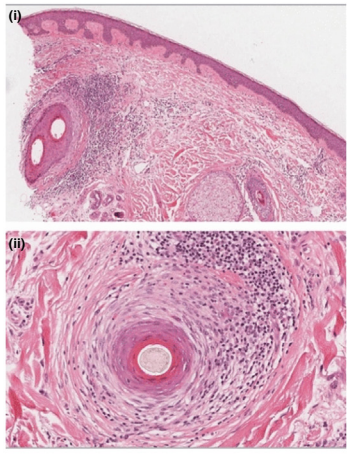
b Shared features



1. Lichenoid, perifollicular lymphocytic infiltrate.



2. H&E demonstrating follicular fibrosis and destruction of sebaceous glands.



3. (i) Perifollicular inflammation and interface change localized to the infundibulum. (ii)Squamatization of the basal follicular epithelium, perifollicular fibrosis and inflammation.

Figure 2. Immunohistopathologic characteristics of LPP and FFA. (**a1**) Quantitative display of the median cell counts for all statistically significant results of CD68$^+$ macrophages in the key parts of follicular anatomy involved in LPP group, FFA group, and control groups (Harries et al., 2020). (**a2**) Photographic images of CD68 positivity at the hair follicle bulge region in LPP and FFA (Harries et al., 2020). (**a3**) CD68 macrophage M1 marker is downregulated, and M2 marker CD163 is upregulated in lesional LPP skin compared with that in nonlesional LPP and FFA. The percentages of macrophages (CD68$^+$) expressing each marker in the CTS were calculated and expressed as the fold change calculated from patient-matched nonlesional skin (Harries et al., 2020). (**b1, b2, b3**) H&E staining showing the key similarities of histopathology samples of LPP and FFA (Chiang et al., 2012). APM, arrector pili muscle; CTS, connective tissue sheath; FFA, frontal fibrosing alopecia; LPP, lichen planopilaris.

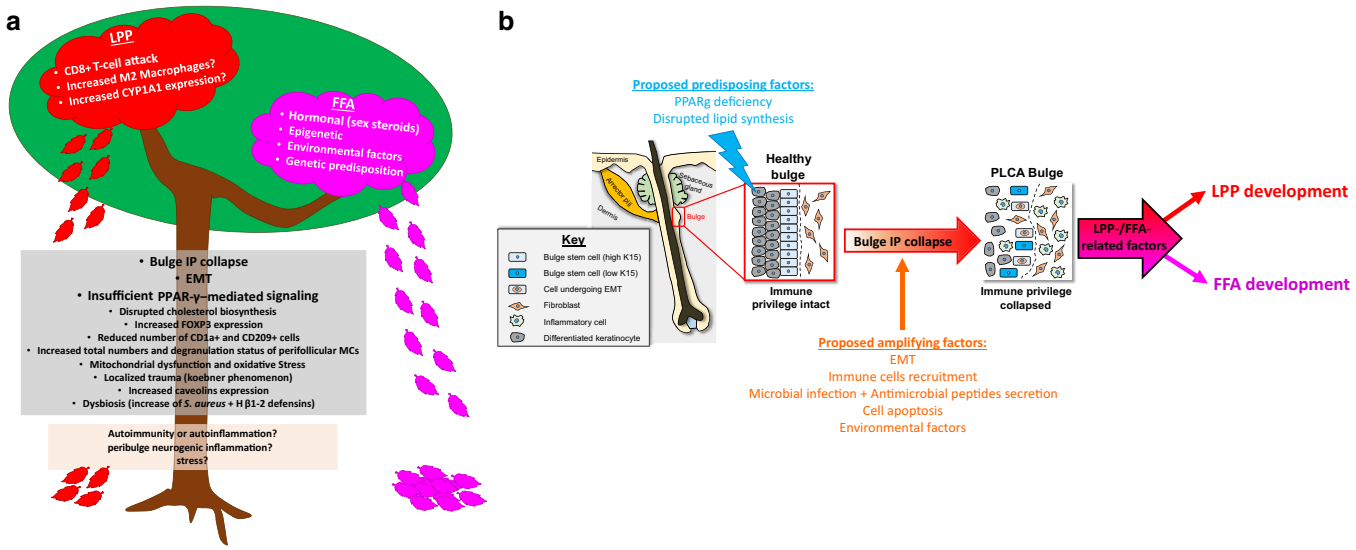


Figure 3. LPP and FFA: similarities and differences in the pathobiology tree. (**a**) Cartoon (modified from Harries et al. [2018]) exhibits the actual known key pathways shared by LPP and FFA, such as PPAR-γ deficiency, immune privilege collapse and EMT, but also additional pathways more recently identified such as dysbiosis, increased FOXP3 expression, or mitochondrial dysfunction. Despite sharing many common pathways, these two hair diseases diverge at some point. Indeed, $CD8^+$ T cells have been shown to attack the bulge of LPP, and recent evidence tends also to show that LPP HFs showed increased M2 macrophage number but also increased CYP1A1 expression. On the other hand, FFA development is associated with environmental and epigenetic factors as well as abnormal hormonal (steroids) levels. (**b**) Proposed diagram (modified from Jozic et al. [2021b]) of the key processes involved in LPP and FFA development from healthy HFs until the occurrence of permanent scarring alopecia. We showed the progression of healthy HFs possessing some predisposing factors (in blue). When these predisposed HFs are affected by any of the amplifying factors (in orange), HF IP will collapse. At this point, specific factors related to FFA or LPP will guide the HFs in one or the other pathology. EMT, epithelial–mesenchymal transition; FFA, frontal fibrosing alopecia; HF, hair follicle; IP, immune privilege; K15, keratin 15; LPP, lichen planopilaris; MC, mast cells; PPAR-γ, peroxisome proliferator-activated receptor-γ.

include skin trauma due to hair transplantation (triggering LPP development) and/or face lift surgery (inducing FFA) (Chiang et al., 2012; Lee et al., 2021; Vañó-Galván et al., 2019b), psychoemotional stress and stress mediators (e.g., substance P [SP] induces neurogenic inflammation and immune privilege [IP] collapse of human scalp HFs [Peters et al., 2007], whereas noradrenaline can induce the proliferation and thus exhaustion of HF melanocytes stem cells (SCs) in mice [Zhang et al., 2020]; indeed, LPP and FFA HFs show loss of melanocytes [Lin et al., 2017; Salas-Callo et al., 2021]), and certain leave-on cosmetics whose relevance in FFA is currently intensely being debated (Aldoori et al., 2016; Debroy Kidambi et al., 2017; Strazzulla et al., 2017). All these may trigger the recruitment of a pathogenic immune cell infiltrate to the HF, possibly along with dysbiosis of the HF microbiome (Constantinou et al., 2021b; Lousada et al., 2021), thus further perpetuating the perifollicular inflammation. Intriguingly, the resulting immune-mediated HF destruction may locally activate and recruit ancestral physiological mechanisms whereby isolated irreversibly damaged or malfunctioning HFs can be individually immune eliminated by macrophage (MAC) infiltration of the bulge (programmed organ deletion) (Eichmüller et al., 1998) but now on a massive pathological scale that affects entire HF collectives in a given skin territory (for discussion, see Harries et al. [2018]).

Although what remains painfully unclear in this scenario is the initiating primary factor(s) that render(s) the bulge of previously healthy or nonlesional HFs (in patients affected by LPP/FFA) susceptible to IP collapse and/or epithelial SC apoptosis and epithelial–mesenchymal transition (EMT) (see the section below); however, peroxisome proliferator–activated receptor-γ (PPAR-γ) dysfunction and dysregulation of PPAR-γ–stimulating lipid mediators have been postulated as such a primary factors (Karnik et al., 2009). PPAR-γ signaling is indeed an important regulator of human HF physiology and a major epithelial SC protectant (see the section below) and is involved in the pathophysiology of several hair diseases (Chéret et al., 2020; Imanishi et al., 2018; Ramot et al., 2020). However, the bulge PPAR-γ expression does not differ substantially between lesional and nonlesional HFs of patients affected by LPP/FFA (Harries et al., 2013). This questions whether insufficient PPAR-γ–mediated signaling really initiates LPP/FFA pathogenesis but does not rule it out either.

The most important genetic FFA study published so far has identified several genes to be associated with FFA, whereas some others were overexpressed in full-thickness lesional skin biopsies (see later) (Tziotzios et al., 2019). Yet, the functional relevance of none of the identified genes has as yet to be established. Therefore, we currently favor the concept that both LPP and FFA are primarily territorial diseases triggered initially by relatively localized intracutaneous pathobiology events, whose clinical phenotype, localization, spread, and course may be modified but is not dictated by environmental, genetic, hormonal, and HF microbiome–related factors and/or leave-on cosmetics (Harries et al., 2018).

Epithelial SC niche immunopathology: The bulge IP collapse concept

All currently available evidence suggests that LPP and FFA both result from immune targeting and eventually the

depletion of the eHFSC reservoir, which ultimately exhausts the HF ability to regenerate and causes loss of HFs. These eHFSCs are located inside the bulge epithelium, an HF compartment that exhibits the classical immune phenotype of a tissue niche that has established a relative IP (Harries et al., 2013; Meyer et al., 2008; Ohyama et al., 2006). IP is specific to certain body sites, including the HF, proximal nail fold, eye, brain, testes, ovaries, and the fetotrophoblast, and provides protection from immunologic attack by the down-regulation of major histocompatibility complex (MHC) class I and β2-microglobulin molecules and by the creation of an immunoinhibitory environment generated by IP guardians such as IL-10, TGFβ1, TGFβ2, α-melanocyte-stimulating hormone (α-MSH), and IGF-1 (Bertolini et al., 2020; Ito et al., 2004b; Paus et al., 2005).

Similar to alopecia areata (AA) where the disease cannot develop without the occurrence of the collapse of the anagen hair bulb IP (Gilhar et al., 2019; 2012), the collapse of bulge IP may be an essential first step in the pathogenesis of LPP and FFA (Harries et al., 2013) because no lesional LPP or FFA HFs have yet been identified that lack bulge IP collapse when the latter was examined. Moreover, in mice, selectively deleting the no danger signal, CD200, a key element of bulge IP (Meyer et al., 2008; Ohyama et al., 2006), in keratin (K) 15^+ eHFSCs induces a murine PCA phenotype that displays the characteristics of both LPP and FFA (Rosenblum et al., 2004). As a therapeutic consequence, rapid restoration of bulge IP would be of paramount clinical importance in the management of both LPP and FFA. Furthermore, IFN-γ, the pathogenic cytokine secreted by $CD8^+$ T cells that attacked the bulge in LPP/FFA promotes bulge IP collapse (Harries et al., 2013; Imanishi et al., 2018). However, this fundamentally important LPP and FFA pathobiology concept requires further confirmation.

Although what remains quite unclear to date is how bulge IP collapse is initiated in the first place, both in LPP and in FFA, and which environmental and/or endogenous signals promote this key pathogenesis event. Although the bulge gene and protein expression profile of established lesional versus nonlesional bulge regions in both patients with LPP and those with FFA is characterized by an upregulation of transcriptional markers of IFN-γ–related signaling (Harries et al., 2013), this does not yet prove that excessive IFN-γ secretion is indeed the proverbial "match that lights the fire." Yet, IFN-γ currently is the best candidate to fit this bill—not the least because IFN-γ–secreting cytotoxic perforin-positive $CD8^+$ T cells seem to be the first immunocytes that can be identified on the crime scene, that is, inside the bulge epithelium of lesional LPP or FFA HFs; in addition, other immunocytes involved in immune-mediated damage of the bulge region, such as $CXCR3^+$ (Harries et al., 2020, 2013) and $FOXP3^+$ T cells, also prominently secrete IFN-γ (Harries et al., 2020).

Nevertheless, other players that have surfaced in the context of AA research might induce bulge IP collapse as well. These include the neuropeptide, SP, which is released from the dense sensory innervation at the level of the bulge and causes neurogenic skin and HF inflammation (Peters et al., 2007) (see later), and possibly also IL-12, which can induce human hair bulb IP collapse. In addition, human HFs are constantly being policed by γδT cells, namely $V\delta1^+$ T lymphocytes, which can recognize the markers of tissue distress such as MICA protein expression through their NKG2D receptors; activation of the latter induces IFN-γ secretion by these cells, followed by IP collapse in the anagen hair bulb (Uchida et al., 2021, 2020). $NKG2D^+$ NK cells can exert very similar functions and thereby induce AA lesions (Gilhar et al., 2013; Ito et al., 2008).

Thus, it deserves to be investigated whether autoantigen-specific $CD8^+$ T cells really are always the very first immunocytes that attack and infiltrate the bulge in LPP or FFA or whether IFN-γ–secreting protagonists of innate or transitional immunity, such as γδTCs or NK cells, first recognize tissue distress signals arising from the bulge epithelium (e.g., in response to trauma, HF dysbiosis, environmental toxins, or allergens that have accumulated in the distal HF epithelium [see later] or to nonspecific danger signals such as selected chemokines secreted by a stressed or damaged bulge epithelium) and then recruit $CD8^+$ T cells only subsequently.

In any case, whether or not this leads to a functionally relevant collapse of bulge IP may determine whether eHFSCs come under attack, for example, by cytotoxic perforin-positive $CD8^+$ T cells (Figure 3b). Intriguingly, this immune attack is not only associated with substantial eHFSC apoptosis. Initially, some of these SCs even seem to enter into the cell cycle (as a frustrated damage–repair attempt?), whereas the apoptotic cell machinery has already been activated, thus further expediting the depletion of the eHFSC niche (Harries et al., 2013). A very similar phenomenon also occurs in human scalp HFs that are being exposed to chemotherapy ex vivo (Piccini et al., 2021; Purba et al., 2019). Thus, human eHFSCs may unfortunately be prone to succumb to SC niche–depletory events, if confronted with cytotoxic cytokines and other agents that the bulge SC niche environment cannot neutralize/inactivate. If further research corroborates this concept, LPP and FFA research is challenged to systematically search for just what these eHFSC cytotoxic agents might be—in addition to the usual suspects, that is, IFN-γ and perforin (Harries et al., 2018, 2013).

LPP-/FFA-associated fibrosis by EMT induction of eHFSCs

Human eHFSCs seem to have yet another Achilles heel: their vulnerability to undergo pathological EMT. Both LPP and FFA are typically associated with scarring/fibrosis (Doche et al., 2020b; Harries et al., 2018; Ocampo-Garza et al., 2021). This cannot be credibly explained by the apoptosis-induced depletion of the epithelial SCs and their progeny because the loss of epithelial cells induces tissue atrophy but not fibrosis. Therefore, it is an important, relatively new LPP/FFA pathobiology concept that the scarring/fibrosis seen in LPP and FFA results at least in part from pathological EMT of eHFSC within the bulge (Chéret et al., 2020; Harries et al., 2018; Imanishi et al., 2018) and not only from pathological fibroblast proliferation and ECM production within the HF mesenchyme and perifollicular dermis.

The bulge epithelium of lesional LPP HFs is characterized by the upregulation of EMT markers such as vimentin and fibronectin and shows ultrastructural signs of EMT. Most importantly, individual $K15^+$ eHFSC can be identified within the bulge epithelia that are double positive for vimentin, a

highly pathological phenomenon compatible with EMT induction. In addition, stimulation of perfectly healthy, organ-cultured human scalp HFs with a cocktail of just four agents well-known to induce EMT in various systems (i.e., the potent E-cadherin antagonist, peptide A, EGF, TGF-β1, and IFN-γ) also does so in the human bulge (Chéret et al., 2020; Imanishi et al., 2018). Interestingly, pathological EMT is also seen when healthy human scalp HFs are treated ex vivo with certain chemotherapeutic agents (Piccini et al., 2021). Thus, it is conceivable that pathological bulge EMT might, on the one hand, result from IP collapse–related excessive IFN-γ secretion but, on the other hand, also from certain environmental or metabolic toxins that can promote eHFSC EMT (yet remain to be identified). In any case, pathological EMT induction within the bulge can explain the LPP-/FFA-associated scarring/fibrosis, at least in part, and is a critical target for early and aggressive therapeutic intervention before eHFSC EMT has progressed beyond the point-of-no-return.

LPP and FFA: Two distinct branches of the same tree?

This discussion brings us back to the vexing initial question of how two microscopically very similar diseases can exhibit such a distinct clinical phenotype (Table 1 and Figures 1 and 2). Using the simplistic image of a PCA pathogenesis tree, we have proposed that LPP and FFA share a common initial pathobiology trunk but then prominently bifurcate into clinically distinct branches, with immune-mediated eHFSC apoptosis and lichenoid inflammatory cell HF infiltrates dominating the picture in LPP, whereas EMT and classical fibrosis phenomena predominate in FFA (Harries et al., 2018) (Figure 3a and b). What exactly dictates into which of these two putative PCA branches, the disease develops in a given patient after the initially shared pathobiology events (i.e., bulge IP collapse, eHFSC apoptosis, and EMT) has evolved. However, there are some plausible contenders that may be involved in driving the proposed bifurcation, such as a certain genetic predisposition favoring the FFA phenotype (see the section below), whereas the pathogenic activities of peribulge MACs might promote the development of the LPP phenotype (Harries et al., 2020) (Figure 2).

These general concepts provide guidance for the development of more effective future LPP and FFA treatment strategies. On this background, we conclude this review by discussing specific genetic, hormonal, and environmental factors in the pathobiology of these PCAs before sketching some novel, pathobiology-based therapeutic approaches that we consider particularly promising.

GENETIC FACTORS

Although reported pediatric cases of LPP are rare, they outnumber the even rarer reported pediatric cases of FFA (>12:3). There are only three reports of pediatric FFA in the literature: twin sisters aged 14 years who developed FFA at age 5 years and a female aged 7 years with FFA (Atarguine et al., 2016). Although the histology of the female aged 7 years was reportedly consistent with FFA, the histology and clinical presentation of what is reported as FFA in the twin sisters is less convincing, showing only depletion of HFs with dermal fibrosis and perivascular infiltrate. In contrast, at least 12 pediatric cases of LPP have been reported, and 33% of these occurred in boys (Christensen et al., 2015). The lack of pediatric FFA cases despite the significant increase in overall FFA numbers strongly suggests that there is a considerable epigenetic influence in FFA development.

However, the relatively high number of familial FFA cases also indicates that a genetic predisposition for FFA is likely, a concept that is further supported by the recent Tziotzios et al. (2019)'s study. At least 50 patients across 15 families have been reported to have familial FFA (Dlova et al., 2013; Junqueira Ribeiro Pereira et al., 2010; Navarro-Belmonte et al., 2015; Porriño-Bustamante et al., 2019; Tziotzios et al., 2015). These familial FFA cases notably include one report of FFA in six sisters (Rocha et al., 2020) and at least seven instances of FFA occurring in male family members. The observed inheritance in these familial FFA cases suggests an autosomal dominant transmission pattern with reduced penetrance. Only one of these reports mentions the potential for common environmental exposures among familial FFA cases, stating that the 10 affected family members either lived in the same home or in the same town; this possibility is not known for the other FFA family cases. One Brazilian study identified susceptibility haplotypes in a cluster of familial cases of FFA and reported that these same haplotypes were identified in five of seven sporadic cases that they included as well (Ramos et al., 2020). Specifically, in the familial cluster of FFA cases in this study, three of four unaffected family members had these alleles present, suggesting a role for the environment in FFA pathogenesis in those who are genetically susceptible. Such a relatively clear genetic predisposition is not documented for LPP (there is only one report of LPP affecting three generations of women in one family [Misiak-Galazka et al., 2016]) and may thus constitute at least one driver in the HF pathology bifurcation toward the FFA phenotype (Figure 3a and b).

What is known about the genetic factors in LPP and FFA? One of the largest genetic studies in LPP was done in 40 Jewish Israeli patients (82.5% of whom were non-Ashkenazi) and 252 controls. Molecular typing revealed that the patients with LPP had a significantly higher frequency of the *DRB1*11* and *DQB1*03* alleles than the controls (Pavlovsky et al., 2015). *DQB1*03* has been implicated as a susceptibility locus for AA and in IP collapse. In yet another study of patients with LPP, increased transcription of HLA *DRB1* and *DQB1* genes was found in affected but not in unaffected scalp tissue. Interestingly, one report of HLA testing in a daughter with LPP and a mother with FFA showed that both had HLA *DRB1* and *DQB1* alleles that were identical, suggesting that LPP and FFA may share a common genetic basis but develop different phenotypes depending on environmental, hormonal, or other influences (Rivas et al., 2015).

In addition, microarray analyses of whole affected and unaffected skin biopsies from patients with LPP showed a significant upregulation in the *CYP1A1* gene (Karnik et al., 2009). The expression of *CYP1A1* is directly controlled by signaling of the AhR, a cellular receptor that plays a role in the processing of xenobiotics, oxidation reactions, and immune regulation, suggesting a role for this receptor in the development of LPP. Increased expression of AhR^{+} cells was also found in the epidermis of unaffected LPP and FFA scalp specimens compared with that in controls, and 30% of

patients with LPP and FFA had increased number of AhR^+ cells on the affected scalp compared with that on the unaffected area (Doche et al., 2020a). A GWAS and meta-analysis in female patients with FFA revealed a significant FFA association at four loci, including a missense variant in *CYP1B1*, a gene that encodes a xenobiotic processing enzyme and aryl hydrocarbon hydroxylase and has been implicated in the regulation of human immune cells. Other alleles, including *HLA-B*07:02* and *ST3GAL1*, were also shown to be associated, suggesting that aberrant antigen processing and T-cell homeostasis may play a role in the development of FFA (Tziotzios et al., 2019).

Unfortunately, because no study has comprehensively investigated and compared molecular typing and genomics in both conditions, we do not really understand yet where the genetics of LPP and FFA overlap (the trunk as shown in Figure 3a) and diverge (LPP vs. FAA branch as shown in Figure 3b). Also unclear is the pathobiological relevance of the haplotypes and the candidate genes. No functional confirmation, for example, through gene silencing of recently reported candidate genes (Tziotzios et al., 2019) in organ-cultured human HFs, has been published, even though this has long been possible and is highly instructive in HF genodermatoses (Samuelov et al., 2012; Sugawara et al., 2012; Tiede et al., 2021), and no persuasive scenario has been proposed on how exactly these genetic elements may contribute to the early stages of FFA versus that of LPP pathogenesis.

OTHER FACTORS

In the venerable history of LPP/FFA pathogenesis discussions (Baibergenova and Donovan, 2013; Harries et al., 2018; Headington, 1996; Kang et al., 2008; Kerkemeyer et al., 2021; Tziotzios et al., 2016), many different potential triggering or aggravating factors besides trauma have been implicated. It remains a wide-open question whether, where, and to which extent the factors discussed in the following sections and listed in Table 2 exert and possibly coalesce in any epigenetic changes that affect LPP/FFA pathogenesis (regrettably, the epigenetic pathology of PCAs essentially is terra incognita).

Endocrine factors

Hormones such as androgens, estradiol, thyroid hormones, and prolactin all prominently regulate both human hair growth and epithelial SC functions (Inui and Itami, 2013; Ohnemus et al., 2006; Paus et al., 2014; Ramot et al., 2021). Among these, the potential role of androgens in FFA has received special attention. The hairline recession in FFA and the frequent concomitant androgenetic alopecia (AGA) that occurs in patients with LPP and FFA have led some authors to propose a role for androgen excess in FFA, largely on the basis of the postmenopausal predominance of affected females (Dawn et al., 2003; Ranasinghe et al., 2017). Although definitive evidence for this hypothesis is missing, reports of clinical benefits seen in some patients treated with 5α-reductase inhibitors (5ARIs) such as dutasteride (Jerjen et al., 2021; Lobato-Berezo et al., 2018; Panchaprateep et al., 2020; Pindado-Ortega et al., 2021; Vañó-Galván et al., 2016) have been interpreted as supporting it. However, the results of retrospective cohort studies of moderate quality where patients were treated with concomitant therapies in addition to 5ARIs and/or serum androgen and estrogen levels were not measured should be interpreted cautiously (Murad and Bergfeld, 2021).

Yet, the involvement of non androgen-dependent scalp hair in LPP and FFA (eyebrows, limb hair) and lack of concomitant hirsutism and acne in this patient population may argue against a major pathogenic role for androgens. That the frontal hairline, the main target HF population in women with FFA, is relatively spared in female, Ludwig-pattern AGA, presumably owing to the decreased density of androgen receptors in female HF at this location further questions a key role of androgens in female FFA development (Grymowicz et al., 2020; Katoulis et al., 2018; MacDonald et al., 2012). One retrospective study of 168 female patients investigated the association of androgen excess or deficiency with LPP and FFA. A total of 69% of the subjects were postmenopausal, and 31% had a history of polycystic ovary syndrome. A total of 41.7% of patients had LPP, 31.5% had FFA, and 26.8% had LPP/FFA overlap. Notably, androgen excess was seen in 40% of patients with LPP and in 35.6% of

Table 2. Frequency of Positive Patch Test Results in Patients with LPP and/or FFA Compared with Rates in the European General Population

Allergen	Prasaad et al., 2020 (N = 42)	Aldoori et al., 2016 (N= 40)	Rocha et al., 2018 (N = 63)	Pastor-Nieto et al., 2021 (N = 36)	Diepgen et al., 2016 (N = 3,119)
Percentage of patients with at least one positive relevant allergen	76%	52.5%	27%	80.5%	27%
Gallates	26.2%			16.6%	
Fragrance Mix I	14.3%	10.0%	5.0%	8.3%	0.9%
Linalool	19.0%	22.5%	8.0%	5.5%	
Limonene	4.8%			13.8%	
Ammonium persulfate	14.3%				
Benzophenone 4	14.3%	12.5%	8.0%		
Benzyl salicylate	4.8%			22%	
Propolis	9.5%			16.6%	
MI/MCI	11.9%	17.5%		2.8%	0.5%
Balsam of Peru	7.1%	12.5%	8.0%	5.5%	0.7%

Abbreviations: FFA, frontal fibrosing alopecia; LPP, lichen planopilaris; MI/MCI, methylisothiazolinone/methylchloroisothiazolinone.

patients with LPP/FFA but surprisingly not in the FFA only group; in contrast, androgen deficiency was seen in 32.1% of patients with FFA (Ranasinghe et al., 2017). In a cross-sectional study of 711 female patients with FFA, 5.6% of women had a history of estrogen deficiency, and 2.3% were exposed to selective estrogen receptor modulators such as tamoxifen or clomiphene (McSweeney et al., 2020). Thus, more robust data are needed before the role of sex steroids in FFA and/or LPP pathogenesis can be fully judged.

Environmental chemical exposure

Several of the earliest cases of follicular spinous eruptions affecting the scalp in the setting of generalized lichen planus—deemed to be the first published cases of LPP—were reported in otherwise healthy postmenopausal women (Little, 1915; Pringle, 1915). However, in 1909, a case of patchy scarring alopecia affecting only the scalp with perifollicular scale and erythema was described in a healthy male lithographer aged 34 years exposed to occupational chlorinated hydrocarbons, heavy metals, and strong acids (Macleod, 1909). Later, another report of a sudden eruption of follicular inflammatory lesions on the abdomen that quickly generalized to involve the scalp was reported in a female aged 43 years just 1 month after undergoing a dilatation and curettage for menorrhagia (Peters, 1939). Perhaps most striking is a recent case of a male construction worker aged 35 years who acutely developed biopsy-proven LPP 2 weeks after high-concentration exposure to trichloroethylene and perchloroethylene during ground intrusive work at a previous dry-cleaning facility site. Despite treatment, this patient had rapid progression and loss of all scalp hair within 3 years (Marks et al., 2019). Although these anecdotal cases reflect atypical and more severe presentations of LPP, the coincident occurrences of LPP after exposure to occupational or perioperative substances raise interest in the potential role of environmental influences in LPP development.

Instead, recent reports have focused mainly on the association between FFA and environmental exposures, likely fostered by reports of the emerging epidemic of FFA cases (Mirmirani et al., 2019) and owing to the distribution of hair loss being in areas of frequent contact with personal care products (PCPs) (moisturizers, cosmetics) and sunscreens. PubMed analysis trends have been used by authors to show the increase in FFA numbers by reporting the surge in FFA publications over time (Mirmirani et al., 2019). However, as of September 2021, similar trends are seen in this PubMed analysis for LPP, with 39 and 609 total articles published through 1994 and 2021, respectively, compared with 1 and 633 articles published on FFA over this same time course. Notably, a 2019 multicenter study of specialty alopecia clinics across four continents reported that the frequency of patients with FFA was 10.8%, followed closely by that of LPP (7.6%) (Vañó-Galván et al., 2019a). Although it is undeniable that cases of FFA have increased over time, it should not be overlooked that LPP diagnoses have similarly risen.

It is also important to consider that since 2010, there has been a significantly increased reporting of adverse effects from haircare products to the United States Food and Drug Administration, with above-average reports of serious health outcomes associated with items used for personal-cleanliness haircare and hair-coloring products (Kwa et al., 2017). Furthermore, three hair product lines have been subjects of class action lawsuits in the United States, namely Brazilian Blowout, Chaz Dean's Wen products, and DevaCurl, with consumers reporting hair loss and scalp inflammation after use of these products (ClassAction.org, 2020). Although these certainly do not prove an association between these products and LPP or FFA development, they do suggest that selected hair products may stimulate immune responses leading to HF pathology, whose downstream effects require further investigation.

PCPs

The increase in the cases of FFA, the distribution of its involvement, and that it largely affects postmenopausal women have stimulated research into the possibility that PCPs could play a role in pathogenesis. The association between FFA and increased use of leave-on facial products, including sunscreens, was initially reported in case-control survey studies. A subset of these patients with FFA underwent patch testing that revealed an increased allergy to fragrance (Aldoori et al., 2016; Debroy Kidambi et al., 2017), and subsequent patch testing studies conducted in other countries in patients with FFA identified other potentially relevant allergens (Aldoori et al., 2016; Pastor-Nieto et al., 2021; Rocha et al., 2018) (Table 2).

Although these studies did not include patients with LPP, another patch testing study of 42 patients with LPP and FFA reported that 76% had at least one relevant positive allergic reaction to ingredients in their PCPs used on the head and neck (Prasad et al., 2020). There were no differences in the rates of allergy between patients with LPP and those with FFA, and the most common allergens identified were gallates, linalool, and Fragrance Mix I (Table 2). Notably, diligent avoidance of known allergens for 3 months led to decreased scalp symptoms and clinical signs of LPP and FFA. Most remarkable about these contact allergy reports in patients with LPP and FFA is how the rates of allergy compare with what is known about the rates of these allergens in the general population. In a study of patch testing responses in the European general population, only 0.9% of people had positive reactions to Fragrance Mix I compared with 14.3%, 10%, 5%, and 8.3% reported in the LPP and FFA populations (Aldoori et al., 2016; Pastor-Nieto et al., 2021; Prasad et al., 2020; Rocha et al., 2018) (Table 2).

Further research into the exact role of these allergens or other PCP ingredients and the downstream effects of sensitization to these agents on HF biology and immune status is necessary before the ongoing controversial debate on the role of leave-on cosmetics in LPP and/or FFA pathogenesis (Aldoori et al., 2016; Debroy Kidambi et al., 2017; Strazzulla et al., 2017; Tavakolpour et al., 2019) can be laid to rest, in one way or another. Certainly, it would be instructive to clarify in this context whether any of the incriminated candidate agents impairs bulge IP and/or eHFSC functions by testing these directly in full-length HF organ culture (Chéret et al., 2020; Purba et al., 2019).

Odorants and olfactory receptors

Many leave-on cosmetics contain natural or synthetic odorants, for which human scalp HFs prominently express

functional olfactory receptors and whose stimulation both regulates hair growth (Chéret et al., 2018) and can affect tissue pathology in various systems (Maßberg and Hatt, 2018). Olfactory receptor stimulation with a synthetic odorant contained in many perfumes and aftershaves also stimulates the production of potent antimicrobial peptides in human scalp HFs ex vivo (Chéret et al., 2018) and thus may impact the composition of the HF microbiome (Lousada et al., 2021). Olfactory receptors are expressed by many immune cell populations, including $CD8^+$ T cells and MACs (Clark et al., 2016), and activation of specific MAC surface olfactory receptors can induce chemokine secretion (Li et al., 2013) and polarization into M2 MACs (Vadevoo et al., 2021). This is interesting because the M2 phenotype is preferentially increased around lesional LPP HFs (Figure 2a) (Harries et al., 2020), raising the question whether this or other olfactory receptors might be involved in the development of LPP.

Recently, we found that patients with LPP are allergic to gallates and linalool, an odorant known to specifically activate OR1C1 (Mainland et al., 2015) and that there was a direct correlation between the use of products containing these molecules and disease development (Prasad et al., 2020). Interestingly, OR1C1 has been found to be expressed in the testis (Flegel et al., 2015), another key site of IP such as the HF bulge. Therefore, the potential role of odorant-induced, olfactory receptor–dependent mechanisms in LPP/FFA chemosensation pathobiology deserves systematic exploration.

Caveolins/caveolae

Most recently, specialized membrane microdomains (caveolae) have also emerged as a promising, previously overlooked target in future LPP/FFA management. The scaffolding protein, CAV1, a key structural component of caveolae, not only colocalizes with K15 in the outer root sheath and eHFSCs of human scalp HFs, but its expression is also significantly elevated in lesional FFA compared with that in healthy scalp HFs (Jozic et al., 2021b). Furthermore, it is well established that CAV1 inhibits TGFβ- and α-MSH–mediated (He et al., 2015) signaling and thus antagonizes the activity of these key guardians of HF IP.

In addition, CAV1 upregulates the expression of IFN-γ, the key inducer of bulge HF IP collapse, as well as SP and MICA (Oakley et al., 2009; Stang et al., 1997; Tomassian et al., 2011). Moreover, the SP receptor, neurokinin (NK1), localizes to caveolae, and disruption of caveolae by cholesterol-depleting agents significantly reduces SP reactivity and activation of NK1 receptor in mice (Monastyrskaya et al., 2005). Additional arguments in support of elucidating the role of caveolins and caveolae in FFA/LPP pathobiology arise from the fact that CAV1 expression is upregulated during EMT (Bailey and Liu, 2008; Gai et al., 2014; Liang et al., 2014) and that the overexpression of CAV1 can lead to the downregulation of E-cadherin and upregulation of vimentin (Cokakli et al., 2009) and thus promotes EMT. Thus, pharmacologically downregulating caveolins might help to protect the bulge from both IP collapse and pathological EMT (Jozic et al., 2021b).

Dysbiosis

There is an increasing interest in the role of HF dysbiosis in various hair diseases, such as AA and AGA, whereas very little is as yet known about the HF microbiome in LPP and FFA (Constantinou et al., 2021a, 2021b; Gaber et al., 2015; Lousada et al., 2021; Pinto et al., 2019; Polak-Witka et al., 2020). Because *Staphylococcus aureus* overcolonization is thought to be one of the main pathogenic factors in the neutrophilic PCA, folliculitis decalvans (Chiarini et al., 2008; Otberg et al., 2008), it is important to characterize the effect of bacterial colonization and HF dysbiosis also on LPP and FFA.

Interestingly, in female patients with LPP and FFA, *Cutibacterium acnes* reportedly is absent from the lesional FFA scalp surface but was present on LPP lesional scalp and in healthy controls (Constantinou et al., 2021b). Instead, *Actinobacteria* were significantly reduced in lesional skin of both patients with FFA and those with LPP compared with that in healthy controls, whereas the amount of *Firmicutes* was strongly upregulated. Moreover, *S. aureus* was the most abundant bacteria in plucked lesional hair shafts from lesional LPP and FFA areas compared with that from healthy controls, suggesting a role for an imbalance between these bacterial species in the development of these PCAs (Constantinou et al., 2021b). This was accompanied by a strong upregulation of both β-defensin 1 and 2 in patients with LPP and FFA (these β-defensins are well-known T-cell attractants [Kanda et al., 2011; Niyonsaba et al., 2004]). Thus, dissecting the role of HF dysbiosis and the related abnormalities in chemokine secretion, bulge expression of danger signals such as MICA, and changes in the local production of proinflammatory antimicrobial peptides in the early stages of LPP/FFA pathogenesis promise to be a particularly fertile and translationally relevant research frontier.

Stress and neurogenic inflammation

Although our understanding of how psychological stress and hair loss might be related is still quite incomplete (Paus and Arck, 2009), human HFs exhibit a fully functional, local hypothalamic–pituitary–adrenal axis (Ito et al., 2005), including the key stress-related neurohormone, corticotropin-releasing hormone (CRH) (Ito et al., 2004a), which promotes perifollicular mast cell degranulation and the local maturation of mast cells from resident progenitors (Ito et al., 2010). Thus, activation of this intrafollicular neuroendocrine stress responses axis by perceived stress may promote perifollicular neurogenic inflammation, thereby facilitating bulge IP collapse in LPP and FFA.

In mice, perceived stress rapidly induces prominent perifollicular neurogenic inflammation that centers around the bulge region; causes premature HF regression (catagen induction); is dependent on NGF, mast cells, and signaling through the SP receptor, NK1 (Arck et al., 2005, 2001); and also upregulates intrafollicular CRH expression. SP^+ nerve fibers are densely situated around the human HF bulge (Peters et al., 2001), and SP is a known fibroblast GF and can promote fibrosis (Słoniecka and Danielson, 2019). Moreover, SP induces (bulb) IP collapse also in human HFs where it activates perifollicular mast cells and upregulates HF production of the mast cell secretagogue, NGF, and expression

of p75NTR (Peters et al., 2007), whose activation by NGF triggers the apoptosis of HF keratinocytes (KCs); SP also stimulates TNF-α release, which further promotes HF KC apoptosis and catagen development (Botchkarev et al., 1998; Paus et al., 1994; Tron et al., 1990). Furthermore, SP greatly increases the number of $CD68^+$ tissue-resident MACs in human skin (Gherardini et al., 2020), whose number is significantly increased around the bulge of LPP, notably more than around FFA-affected scalp HFs (Figure 2a) (Harries et al., 2020). Therefore, SP-dependent neurogenic (stress-induced?) peribulbar inflammation could also play a role in triggering and/or aggravating LPP and FFA pathobiology; however, this remains to be conclusively shown.

FUTURE DIRECTIONS AND THERAPEUTIC INTERVENTIONS

On the basis of our limited current understanding of LPP and FFA pathobiology (Figure 3a and b), it is possible to envision novel therapeutic intervention strategies that could greatly enhance the arsenal for managing these disfiguring PCAs in the future. To conclude, we briefly highlight some particularly promising avenues for how we might translate recent LPP/FFA pathobiology insights into concrete therapeutic benefits.

Arguably, the lowest-hanging fruit in substantially advancing both LPP and FFA therapy is to finally develop a good topical application vehicle for tacrolimus (FK506) and similar immunophilin ligands that greatly enhances HF penetration. Because FK506 both prevents experimentally induced IP collapse in the human anagen hair bulb and promotes HF IP restoration ex vivo (Ito et al., 2004b), it is to be expected that it will also do so in the (more easily accessible) bulge—if it can only reach a sufficient concentration there. That FK506 treatment with a suboptimal vehicle reportedly already has some therapeutic benefit in selected patients with FFA or LPP (Blazek and Megahed, 2008; Giorgio et al., 2021; Mahmoudi et al., 2022) strongly encourages one to pursue HF-targeting vehicle development for this drug and other candidate bulge IP guardians, such as extended-activity α-MSH (afamelanotide) (Ito et al., 2004b), which might be repurposed for topical LPP/FFA treatment.

Given the potential role of SP and NK1 in peribulge neurogenic inflammation, it also deserves to be tested whether clinically available NK1 antagonists such as aprepitant (Chen et al., 2019) can be repurposed in the management of LPP/FFA.

If the proposed role for caveolins in FFA pathogenesis (Jozic et al., 2021b) is confirmed, this warrants investigation whether topical perturbation of intrafollicular CAV1, either pharmacologically (e.g., through cyclodextrins/statins) (Jozic et al., 2021a, 2019; Sawaya et al., 2019) or by nanoparticle-mediated small interfering RNA delivery, can halt the—often relentless—progression of FFA/LPP and can be used as an auxiliary therapy to the other candidate therapeutics discussed in this paper. Interestingly, the OR2AT4 agonist, Sandalore, which prolongs anagen ex vivo (Chéret et al., 2018), also downregulates the expression of CAV1 at both mRNA and protein levels (Chéret et al., 2020; Jozic et al., 2021b). Besides targeting CAV1 therapeutically, it may also be an overlooked candidate biomarker of disease progression and activity (Jozic et al., 2021b).

The PPAR-γ modulator, NAGED, not only prevents and partially reverses experimentally induced EMT in the human bulge (Imanishi et al., 2018) and upregulates K15 expression in eHFSCs ex vivo (Ramot et al., 2014) but also protects $K15^+$ eHFSC from apoptosis, reduces the number of $CD8^+$ and $MHCII^+$ cells in the bulge region of LPP HFs, and reduces EMT ex vivo (Chéret et al., 2020). Preliminary recent evidence suggests that the bulge of lesional LPP HFs contains dysfunctional mitochondria, including the downregulation of the key TFAM (Hardman-Smart et al., 2020). Because TFAM is upregulated by PPAR-γ (Miglio et al., 2009), PPAR-γ agonists/modulators may also help to prevent or reverse LPP-associated mitochondrial dysfunction.

Additional future interventions should consider prophylactic avoidance of potentially immune-stimulating environmental factors, including allergenic and certain olfactory receptors–stimulating fragrances in PCPs, namely in genetically or otherwise FFA- or LPP-predisposed individuals. This will become mandatory if experimental evidence becomes available that some fragrances stimulate pathogenic MAC and dendritic cell activities at the level of the bulge and/or alter the physiological composition of the HF microbiome through olfactory receptors–controlled changes in the intrafollicular production of antimicrobial peptides (Chéret et al., 2018).

Importantly, directions for future research must investigate the genetic and pathogenic mechanisms of LPP, FFA, and LPP/FFA overlap in tandem because this is the only way that we will truly begin to appreciate how these conditions are similar and where they diverge. For example, when the genetics of FFA are examined using one method and the genetics of LPP are evaluated in a different way, an important opportunity is missed to understand the similarities and differences between these conditions. Robust research will rely heavily on diagnoses performed by expert dermatologist hair specialists collaborating with colleagues in basic science to yield comprehensive data from reliable samples. Correlating the clinical features of patients with LPP and/or FFA who provide such research samples, including the degree of severity and disease activity, will provide important information to help guide the interpretation of disease processes. It is only through such vigorous clinical and scientific collaboration that the much needed answers for our elusive questions surrounding LPP and FFA will finally become clearer.

In summary, this review shows that refocusing attention on the pathobiology of LPP and FFA along the system of coordinates delineated here and the specific suggestions we have made has substantial translational value. Indeed, it promises to greatly accelerate the development of long-awaited, much more effective LPP/FFA therapies and will likely supply us with robust molecular biomarkers of both, disease activity/subtype and response to therapy.

Data availability statement

No datasets were generated or analyzed during this study.

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Visualization: MMS, RP, EP, JC, IJ; Writing - Original Draft Preparation: MMS, RP; Writing - Review and Editing: EP, JC, IJ

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CONFLICT OF INTEREST

For the record, RP is the chief executive officer of a skin and hair research company (www.monasteriumlab.com) that has performed contract research on the impact of peroxisome proliferator–activated receptor-γ and olfactory receptor ligands on human hair follicles but holds no patents and does not develop products in this area. The remaining authors state no conflict of interest.

REFERENCES

Aldoori N, Dobson K, Holden CR, McDonagh AJ, Harries M, Messenger AG. Frontal fibrosing alopecia: possible association with leave-on facial skin care products and sunscreens; a questionnaire study. Br J Dermatol 2016;175:762–7.

Arck PC, Handjiski B, Hagen E, Joachim R, Klapp BF, Paus R. Indications for a "brain-hair follicle axis (BHA)": inhibition of keratinocyte proliferation and up-regulation of keratinocyte apoptosis in telogen hair follicles by stress and substance P. FASEB J 2001;15:2536–8.

Arck PC, Handjiski B, Kuhlmei A, Peters EMJ, Knackstedt M, Peter A, et al. Mast cell deficient and neurokinin-1 receptor knockout mice are protected from stress-induced hair growth inhibition. J Mol Med (Berl) 2005;83:386–96.

Atarguine H, Hocar O, Hamdaoui A, Akhdari N, Amal S. [Frontal fibrosing alopecia: report on three pediatric cases]. Arch Pediatr 2016;23:832–5.

Baibergenova A, Donovan J. Lichen planopilaris: update on pathogenesis and treatment. Skinmed 2013;11:161–5.

Bailey KM, Liu J. Caveolin-1 up-regulation during epithelial to mesenchymal transition is mediated by focal adhesion kinase. J Biol Chem 2008;283:13714–24.

Bertolini M, McElwee K, Gilhar A, Bulfone-Paus S, Paus R. Hair follicle immune privilege and its collapse in alopecia areata. Exp Dermatol 2020;29:703–25.

Blazek C, Megahed M. [Lichen planopilaris. Successful treatment with tacrolimus]. Hautarzt 2008;59:874–7.

Bolduc C, Sperling LC, Shapiro J. Primary cicatricial alopecia: lymphocytic primary cicatricial alopecias, including chronic cutaneous lupus erythematosus, lichen planopilaris, frontal fibrosing alopecia, and Graham-Little syndrome. J Am Acad Dermatol 2016;75:1081–99.

Botchkarev VA, Botchkarev NV, Albers KM, van der Veen C, Lewin GR, Paus R. Neurotrophin-3 involvement in the regulation of hair follicle morphogenesis. J Invest Dermatol 1998;111:279–85.

Cerqueira ER, Valente N, Sotto MN, Romiti R. Comparative analysis of immunopathological features of lichen planopilaris and female patients with frontal fibrosing alopecia. Int J Trichology 2016;8:197–202.

Chen S, Lu M, Liu D, Yang L, Yi C, Ma L, et al. Human substance P receptor binding mode of the antagonist drug aprepitant by NMR and crystallography. Nat Commun 2019;10:638.

Chéret J, Bertolini M, Ponce L, Lehmann J, Tsai T, Alam M, et al. Olfactory receptor OR2AT4 regulates human hair growth. Nat Commun 2018;9:3624.

Chéret J, Piccini I, Hardman-Smart J, Ghatak S, Alam M, Lehmann J, et al. Preclinical evidence that the PPARγ modulator, N-Acetyl-GED-0507-34-Levo, may protect human hair follicle epithelial stem cells against lichen planopilaris-associated damage. J Eur Acad Dermatol Venereol 2020;34:e195–7.

Chiang YZ, Bundy C, Griffiths CEM, Paus R, Harries MJ. The role of beliefs: lessons from a pilot study on illness perception, psychological distress and quality of life in patients with primary cicatricial alopecia. Br J Dermatol 2015;172:130–7.

Chiang YZ, Tosti A, Chaudhry IH, Lyne L, Farjo B, Farjo N, et al. Lichen planopilaris following hair transplantation and face-lift surgery. Br J Dermatol 2012;166. 666–370.

Chiarini C, Torchia D, Bianchi B, Volpi W, Caproni M, Fabbri P. Immunopathogenesis of folliculitis decalvans: clues in early lesions. Am J Clin Pathol 2008;130:526–34.

Christensen KN, Lehman JS, Tollefson MM. Pediatric lichen planopilaris: clinicopathologic study of four new cases and a review of the literature. Pediatr Dermatol 2015;32:621–7.

Clark AA, Nurmukhambetova S, Li X, Munger SD, Lees JR. Odorants specifically modulate chemotaxis and tissue retention of CD4+ T cells via cyclic adenosine monophosphate induction. J Leukoc Biol 2016;100:699–709.

ClassAction.org. Class action alleges DevaCurl hair products contain several 'Known' allergens, irritants. https://www.classaction.org/news/class-action-alleges-devacurl-hair-products-contain-several-known-allergens-irritants; 2020. (accessed October 4, 2021).

Cokakli M, Erdal E, Nart D, Yilmaz F, Sagol O, Kilic M, et al. Differential expression of Caveolin-1 in hepatocellular carcinoma: correlation with differentiation state, motility and invasion. BMC Cancer 2009;9:65.

Constantinou A, Kanti V, Polak-Witka K, Blume-Peytavi U, Spyrou GM, Vogt A. The potential relevance of the microbiome to hair physiology and regeneration: the emerging role of metagenomics. Biomedicines 2021a;9:236.

Constantinou A, Polak-Witka K, Tomazou M, Oulas A, Kanti V, Schwarzer R, et al. Dysbiosis and enhanced beta-defensin production in hair follicles of patients with lichen planopilaris and frontal fibrosing alopecia. Biomedicines 2021b;9:266.

Dadkhahfar S, Araghi F, Tabary M, Moravvej H. Considerations of managing lichen planopilaris with hydroxychloroquine during the COVID-19 pandemic. J Drugs Dermatol 2020;19:679–80.

Dawn G, Holmes SC, Moffat D, Munro CS. Post-menopausal frontal fibrosing alopecia. Clin Exp Dermatol 2003;28:43–5.

Debroy Kidambi A, Dobson K, Holmes S, Carauna D, Del Marmol V, Vujovic A, et al. Frontal fibrosing alopecia in men: an association with facial moisturizers and sunscreens. Br J Dermatol 2017;177:260–1.

Diepgen TL, Ofenloch RF, Bruze M, Bertuccio P, Cazzaniga S, Coenraads PJ, et al. Prevalence of contact allergy in the general population in different European regions. Br J Dermatol 2016;174:319–29.

Dlova N, Goh CL, Tosti A. Familial frontal fibrosing alopecia. Br J Dermatol 2013;168:220–2.

Doche I, Pagliari C, Hordinsky MK, Wilcox GL, Rivitti-Machado MCM, Romiti R, et al. Overexpression of the aryl hydrocarbon receptor in frontal fibrosing alopecia and lichen planopilaris: a potential pathogenic role for dioxins?: an investigational study of 38 patients. J Eur Acad Dermatol Venereol 2020a;34:e326–9.

Doche I, Wilcox GL, Ericson M, Valente NS, Romiti R, McAdams BD, et al. Evidence for neurogenic inflammation in lichen planopilaris and frontal fibrosing alopecia pathogenic mechanism. Exp Dermatol 2020b;29:282–5.

Du X, Li Y, Zhu Q, Zhu J, Xu W, Li Z, et al. Focal and diffuse fibrosing alopecias: classical lichen planopilaris, frontal fibrosing alopecia, fibrosing alopecia with a pattern distribution, cicatricial pattern hair loss, and lichen planopilaris diffuse pattern. JAAD Case Rep 2020;6:403–10.

Eichmüller S, van der Veen C, Moll I, Hermes B, Hofmann U, Müller-Röver S, et al. Clusters of perifollicular macrophages in normal murine skin: physiological degeneration of selected hair follicles by programmed organ deletion. J Histochem Cytochem 1998;46:361–70.

Fatemi Naeini F, Mohaghegh F, Jelvan M, Asilian A, Saber M. Cyclosporine or methotrexate, which one is more promising in the treatment of lichen planopilaris?; a comparative clinical trial. Int Immunopharmacol 2020;86:106765.

Fertig R, Tosti A. Frontal fibrosing alopecia treatment options. Intractable Rare Dis Res 2016;5:314–5.

Fertig RM, Hu S, Maddy AJ, Balaban A, Aleid N, Aldahan A, et al. Medical comorbidities in patients with lichen planopilaris, a retrospective case-control study. Int J Dermatol 2018;57:804–9.

Flegel C, Vogel F, Hofreuter A, Schreiner BSP, Osthold S, Veitinger S, et al. Characterization of the olfactory receptors expressed in human spermatozoa. Front Mol Biosci 2015;2:73.

Gaber HD, Mohamed AM, Abdel Gaber RM. Presence of Alternaria in scalp of patients with alopecia areata: triggering factor or coexistence? J Life Sci 2015;10:341–5.

Gai X, Lu Z, Tu K, Liang Z, Zheng X. Caveolin-1 is up-regulated by GLI1 and contributes to GLI1-driven EMT in hepatocellular carcinoma. PLoS One 2014;9:e84551.

Gálvez-Canseco A, Sperling L. Lichen planopilaris and frontal fibrosing alopecia cannot be differentiated by histopathology. J Cutan Pathol 2018;45:313–7.

Gherardini J, Uchida Y, Hardman JA, Chéret J, Mace K, Bertolini M, et al. Tissue-resident macrophages can be generated de novo in adult human skin from resident progenitor cells during substance P-mediated neurogenic inflammation ex vivo. PLoS One 2020;15:e0227817.

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

Gilhar A, Keren A, Shemer A, d'Ovidio R, Ullmann Y, Paus R. Autoimmune disease induction in a healthy human organ: a humanized mouse model of alopecia areata. J Invest Dermatol 2013;133:844–7.

Gilhar A, Laufer-Britva R, Keren A, Paus R. Frontiers in alopecia areata pathobiology research. J Allergy Clin Immunol 2019;144:1478–89.

Giorgio CM, Briatico G, Licata G, Babino G, Di Brizzi EV, Pellerone S, et al. Frontal fibrosing alopecia: a successful treatment with tacrolimus 0,2% in topical solution [e-pub ahead of print]. Ital J Dermatol Venerol 2021. https://doi.org/10.23736/S2784-8671.21.07056-0 (accessed October 4, 2021).

Griggs J, Trüeb RM, Gavazzoni Dias MFR, Hordinsky M, Tosti A. Fibrosing alopecia in a pattern distribution. J Am Acad Dermatol 2021;85:1557–64.

Grymowicz M, Rudnicka E, Podfigurna A, Napierala P, Smolarczyk R, Smolarczyk K, et al. Hormonal effects on hair follicles. Int J Mol Sci 2020;21:E5342.

Hardman-Smart JA, Purba TS, Panicker S, Farjo B, Farjo N, Harries MJ, et al. Does mitochondrial dysfunction of hair follicle epithelial stem cells play a role in the pathobiology of lichen planopilaris? Br J Dermatol 2020;183:964–6.

Harries M, Hardman J, Chaudhry I, Poblet E, Paus R. Profiling the human hair follicle immune system in lichen planopilaris and frontal fibrosing alopecia: can macrophage polarization differentiate these two conditions microscopically? Br J Dermatol 2020;183:537–47.

Harries MJ, Jimenez F, Izeta A, Hardman J, Panicker SP, Poblet E, et al. Lichen planopilaris and frontal fibrosing alopecia as model epithelial stem cell diseases. Trends Mol Med 2018;24:435–48.

Harries MJ, Meyer K, Chaudhry I, E Kloepper J, Poblet E, Griffiths CE, et al. Lichen planopilaris is characterized by immune privilege collapse of the hair follicle's epithelial stem cell niche. J. Pathol 2013;231:236–47.

He K, Yan X, Li N, Dang S, Xu L, Zhao B, et al. Internalization of the TGF-β type I receptor into caveolin-1 and EEA1 double-positive early endosomes. Cell Res 2015;25:738–52.

Headington JT. Cicatricial alopecia. Dermatol Clin 1996;14:773–82.

Imanishi H, Ansell DM, Chéret J, Harries M, Bertolini M, Sepp N, et al. Epithelial-to-mesenchymal stem cell transition in a human organ: lessons from lichen planopilaris. J Invest Dermatol 2018;138:511–9.

Inui S, Itami S. Androgen actions on the human hair follicle: perspectives. Exp Dermatol 2013;22:168–71.

Ito N, Ito T, Betterman A, Paus R. The human hair bulb is a source and target of CRH. J Invest Dermatol 2004a;122:235–7.

Ito N, Ito T, Kromminga A, Bettermann A, Takigawa M, Kees F, et al. Human hair follicles display a functional equivalent of the hypothalamic-pituitary-adrenal axis and synthesize cortisol. FASEB J 2005;19:1332–4.

Ito N, Sugawara K, Bodó E, Takigawa M, van Beek N, Ito T, et al. Corticotropin-releasing hormone stimulates the in situ generation of mast cells from precursors in the human hair follicle mesenchyme. J Invest Dermatol 2010;130:995–1004.

Ito T, Ito N, Bettermann A, Tokura Y, Takigawa M, Paus R. Collapse and restoration of MHC class-I-dependent immune privilege: exploiting the human hair follicle as a model. Am J Pathol 2004b;164:623–34.

Ito T, Ito N, Saatoff M, Hashizume H, Fukamizu H, Nickoloff BJ, et al. Maintenance of hair follicle immune privilege is linked to prevention of NK cell attack. J Invest Dermatol 2008;128:1196–206.

Jerjen R, Pinczewski J, Sinclair R, Bhoyrul B. Clinicopathological characteristics and treatment outcomes of fibrosing alopecia in a pattern distribution: a retrospective cohort study. J Eur Acad Dermatol Venereol 2021;35:2440–7.

Jozic I, Abujamra BA, Elliott MH, Wikramanayake TC, Marjanovic J, Stone RC, et al. Glucocorticoid-mediated induction of caveolin-1 disrupts cytoskeletal organization, inhibits cell migration and re-epithelialization of non-healing wounds. Commun Biol 2021a;4:757.

Jozic I, Chéret J, Abujamra BA, Miteva M, Gherardini J, Paus R. A cell membrane-level approach to cicatricial alopecia management: is Caveolin-1 a viable therapeutic target in frontal fibrosing alopecia? Biomedicines 2021b;9:572.

Jozic I, Sawaya AP, Pastar I, Head CR, Wong LL, Glinos GD, et al. Pharmacological and genetic inhibition of caveolin-1 promotes epithelialization and wound closure. Mol Ther 2019;27:1992–2004.

Junqueira Ribeiro Pereira AF, Vincenzi C, Tosti A. Frontal fibrosing alopecia in two sisters. Br J Dermatol 2010;162:1154–5.

Kanda N, Kamata M, Tada Y, Ishikawa T, Sato S, Watanabe S. Human β-defensin-2 enhances IFN-γ and IL-10 production and suppresses IL-17 production in T cells. J Leukoc Biol 2011;89:935–44.

Kang H, Alzolibani AA, Otberg N, Shapiro J. Lichen planopilaris. Dermatol Ther 2008;21:249–56.

Karnik P, Tekeste Z, McCormick TS, Gilliam AC, Price VH, Cooper KD, et al. Hair follicle stem cell-specific PPARgamma deletion causes scarring alopecia. J Invest Dermatol 2009;129:1243–57.

Katoulis AC, Diamanti K, Damaskou V, Pouliakis A, Bozi E, Koufopoulos N, et al. Decreased melanocyte counts in the upper hair follicle in frontal fibrosing alopecia compared to lichen planopilaris: a retrospective histopathologic study. J Eur Acad Dermatol Venereol 2020;35:e343–5.

Katoulis AC, Diamanti K, Sgouros D, Liakou AI, Bozi E, Avgerinou G, et al. Is there a pathogenetic link between frontal fibrosing alopecia, androgenetic alopecia and fibrosing alopecia in a pattern distribution? J Eur Acad Dermatol Venereol 2018;32:e218–20.

Kerkemeyer KLS, Eisman S, Bhoyrul B, Pinczewski J, Sinclair RD. Frontal fibrosing alopecia. Clin Dermatol 2021;39:183–93.

Kurzeja M, Czuwara J, Walecka I, Olszewska M, Rudnicka L. Features of classic lichen planopilaris and frontal fibrosing alopecia in reflectance confocal microscopy: a preliminary study. Skin Res Technol 2021;27:266–71.

Kwa M, Welty LJ, Xu S. Adverse events reported to the US Food and Drug Administration for cosmetics and personal care products. JAMA Intern Med 2017;177:1202–4.

Lee JA, Levy DA, Patel KG, Brennan E, Oyer SL. Hair transplantation in frontal fibrosing alopecia and lichen planopilaris: a systematic review. Laryngoscope 2021;131:59–66.

Li JJ, Tay HL, Plank M, Essilfie AT, Hansbro PM, Foster PS, et al. Activation of olfactory receptors on mouse pulmonary macrophages promotes monocyte chemotactic protein-1 production. PLoS One 2013;8:e80148.

Liang W, Hao Z, Han JL, Zhu DJ, Jin ZF, Xie WL. CAV-1 contributes to bladder cancer progression by inducing epithelial-to-mesenchymal transition. Urol Oncol 2014;32:855–63.

Lin J, Valdebran M, Bergfeld W, Conic RZ, Piliang M, Atanaskova Mesinkovska NA. Hypopigmentation in frontal fibrosing alopecia. J Am Acad Dermatol 2017;76:1184–6.

Little EG. Folliculitis decalvans et atrophicans. Proc R Soc Med 1915;8:139–41.

Lobato-Berezo A, March-Rodríguez A, Deza G, Bertolín-Colilla M, Pujol RM. Frontal fibrosing alopecia after antiandrogen hormonal therapy in a male patient. J Eur Acad Dermatol Venereol 2018;32:e291–2.

Lousada MB, Lachnit T, Edelkamp J, Rouillé T, Ajdic D, Uchida Y, et al. Exploring the human hair follicle microbiome. Br J Dermatol 2021;184:802–15.

Ma SA, Imadojemu S, Beer K, Seykora JT. Inflammatory features of frontal fibrosing alopecia. J Cutan Pathol 2017;44:672–6.

MacDonald A, Clark C, Holmes S. Frontal fibrosing alopecia: a review of 60 cases. J Am Acad Dermatol 2012;67:955–61.

Macleod JMH. Case of pseudo-pelade (Brocq) or cicatricial alopecia, affecting chiefly the vertex of the scalp. Proc R Soc Med 1909;2:75–6.

Mahmoudi H, Rostami A, Tavakolpour S, Nili A, Teimourpour A, Salehi Farid A, et al. Oral isotretinoin combined with topical clobetasol 0.05% and tacrolimus 0.1% for the treatment of frontal fibrosing alopecia: a randomized controlled trial. J Dermatolog Treat 2022;33:284–90.

Mainland JD, Li YR, Zhou T, Liu WLL, Matsunami H. Human olfactory receptor responses to odorants. Sci Data 2015;2:150002.

Marks DH, Hagigeorges D, Manatis-Lornell AJ, Foreman RK, Senna MM. Development of lichen planopilaris-like alopecia following occupational exposure to trichloroethylene and tetrachloroethylene. Skin Appendfage Disord 2019;5:374–8.

Maßberg D, Hatt H. Human olfactory receptors: novel cellular functions outside of the nose. Physiol Rev 2018;98:1739–63.

McSweeney SM, Christou EAA, Dand N, Boalch A, Holmes S, Harries M, et al. Frontal fibrosing alopecia: a descriptive cross-sectional study of 711 cases in female patients from the UK. Br. J. Dermatol 2020;183:1136–8.

Meyer KC, Klatte JE, Dinh HV, Harries MJ, Reithmayer K, Meyer W, et al. Evidence that the bulge region is a site of relative immune privilege in human hair follicles. Br J Dermatol 2008;159:1077–85.

Miglio G, Rosa AC, Rattazzi L, Collino M, Lombardi G, Fantozzi R. PPAR-gamma stimulation promotes mitochondrial biogenesis and prevents glucose deprivation-induced neuronal cell loss. Neurochem Int 2009;55: 496–504.

Mirmirani P, Tosti A, Goldberg L, Whiting D, Sotoodian B. Frontal fibrosing alopecia: an emerging epidemic. Skin Appendage Disord 2019;5:90–3.

Misiak-Galazka M, Olszewska M, Rudnicka L. Lichen planopilaris in three generations: grandmother, mother, and daughter - a genetic link? Int J Dermatol 2016;55:913–5.

Monastyrskaya K, Hostettler A, Buergi S, Draeger A. The NK1 receptor localizes to the plasma membrane microdomains, and its activation is dependent on lipid raft integrity. J Biol Chem 2005;280:7135–46.

Murad A, Bergfeld WF. Reply to effectiveness of dutasteride in a large series of patients with frontal fibrosing alopecia in real clinical practice. J Am Acad Dermatol 2021;85:e93.

Navarro-Belmonte MR, Navarro-López V, Ramírez-Boscà A, Martínez-Andrés MA, Molina-Gil C, González-Nebreda M, et al. Case series of familial frontal fibrosing alopecia and a review of the literature. J Cosmet Dermatol 2015;14:64–9.

Niyonsaba F, Ogawa H, Nagaoka I. Human beta-defensin-2 functions as a chemotactic agent for tumour necrosis factor-alpha-treated human neutrophils. Immunology 2004;111:273–81.

Oakley FD, Smith RL, Engelhardt JF. Lipid rafts and caveolin-1 coordinate interleukin-1beta (IL-1beta)-dependent activation of NFkappaB by controlling endocytosis of Nox2 and IL-1beta receptor 1 from the plasma membrane. J Biol Chem 2009;284:33255–64.

Ocampo-Garza SS, Orizaga-Y-Quiroga TL, Olvera-Rodríguez V, Herz-Ruelas ME, Chavez-Alvarez S, Vañó-Galván S, et al. Frontal fibrosing alopecia: is there a link in relatives? Skin Appendage Disord 2021;7:206–11.

Ohnemus U, Uenalan M, Inzunza J, Gustafsson JA, Paus R. The hair follicle as an estrogen target and source. Endocr Rev 2006;27:677–706.

Ohyama M, Terunuma A, Tock CL, Radonovich MF, Pise-Masison CA, Hopping SB, et al. Characterization and isolation of stem cell-enriched human hair follicle bulge cells. J Clin Invest 2006;116:249–60.

Otberg N, Kang H, Alzolibani AA, Shapiro J. Folliculitis decalvans. Dermatol Ther 2008;21:238–44.

Panchaprateep R, Ruxrungtham P, Chancheewa B, Asawanonda P. Clinical characteristics, trichoscopy, histopathology and treatment outcomes of frontal fibrosing alopecia in an Asian population: a retro-prospective cohort study. J Dermatol 2020;47:1301–11.

Pastor-Nieto MA, Gatica-Ortega ME, Sánchez-Herreros C, Vergara-Sánchez A, Martínez-Mariscal J, De Eusebio-Murillo E. Sensitization to benzyl salicylate and other allergens in patients with frontal fibrosing alopecia [published correction appears in Contact Dermatitis 2021;85:385]. Contact Dermatitis 2021;84:423–30.

Paus R, Arck P. Neuroendocrine perspectives in alopecia areata: does stress play a role? J Invest Dermatol 2009;129:1324–6.

Paus R, Langan EA, Vidali S, Ramot Y, Andersen B. Neuroendocrinology of the hair follicle: principles and clinical perspectives. Trends Mol Med 2014;20: 559–70.

Paus R, Lüftl M, Czarnetzki BM. Nerve growth factor modulates keratinocyte proliferation in murine skin organ culture. Br J Dermatol 1994;130: 174–80.

Paus R, Nickoloff BJ, Ito T. A "hairy" privilege. Trends Immunol 2005;26: 32–40.

Pavlovsky L, Israeli M, Sagy E, Berg AL, David M, Shemer A, et al. Lichen planopilaris is associated with HLA DRB1*11 and DQB1*03 alleles. Acta Derm Venereol 2015;95:177–80.

Peters AD. Lichen pilaris seu spinulosus. Proc R Soc Med 1939;32:1031–2.

Peters EM, Botchkarev VA, Botchkareva NV, Tobin DJ, Paus R. Hair-cycle-associated remodeling of the peptidergic innervation of murine skin, and hair growth modulation by neuropeptides. J Invest Dermatol 2001;116: 236–45.

Peters EMJ, Liotiri S, Bodó E, Hagen E, Bíró T, Arck PC, et al. Probing the effects of stress mediators on the human hair follicle: substance P holds central position. Am J Pathol 2007;171:1872–86.

Peterson EL, Gutierrez D, Brinster NK, Lo Sicco KI, Shapiro J. Response of lichen planopilaris to pioglitazone hydrochloride. J Drugs Dermatol 2019;18:1276–9.

Piccini I, Brunken L, Chéret J, Ghatak S, Ramot Y, Alam M, et al. Peroxisome proliferator-activated receptor-γ signaling protects hair follicle stem cells from chemotherapy-induced apoptosis and epithelial-mesenchymal transition. Br J Dermatol 2021;186:129–41.

Pindado-Ortega C, Saceda-Corralo D, Moreno-Arrones ÓM, Rodrigues-Barata AR, Hermosa-Gelbard Á, Jaén-Olasolo P, et al. Effectiveness of dutasteride in a large series of patients with frontal fibrosing alopecia in real clinical practice. J Am Acad Dermatol 2021;84:1285–94.

Pinto D, Sorbellini E, Marzani B, Rucco M, Giuliani G, Rinaldi F. Scalp bacterial shift in alopecia areata. PLoS One 2019;14:e0215206.

Poblet E, Jiménez F, Pascual A, Piqué E. Frontal fibrosing alopecia versus lichen planopilaris: a clinicopathological study. Int J Dermatol 2006;45: 375–80.

Polak-Witka K, Rudnicka L, Blume-Peytavi U, Vogt A. The role of the microbiome in scalp hair follicle biology and disease. Exp Dermatol 2020;29:286–94.

Porriño-Bustamante ML, López-Nevot MÁ, Aneiros-Fernández J, García-Lora E, Fernández-Pugnaire MA, Arias-Santiago S. Familial frontal fibrosing alopecia: a cross-sectional study of 20 cases from nine families. Australas J Dermatol 2019;60:e113–8.

Prasad S, Marks DH, Burns LJ, De Souza B, Flynn EA, Scheinman P, et al. Patch testing and contact allergen avoidance in patients with lichen planopilaris and/or frontal fibrosing alopecia: a cohort study. J Am Acad Dermatol 2020;83:659–61.

Preda-Naumescu A, Bevans SL, Mayo TT. Pediatric lichen planopilaris treated with pioglitazone: a case study and literature review. J Drugs Dermatol 2021;20:779–82.

Pringle JJ. Lichenous eruption for diagnosis (pityriasis rubra pilaris). Proc R Soc Med 1915;8:4–6.

Purba TS, Ng'andu K, Brunken L, Smart E, Mitchell E, Hassan N, et al. CDK4/6 inhibition mitigates stem cell damage in a novel model for taxane-induced alopecia. EMBO Mol Med 2019;11:e11031.

Ramos PM, Garbers LEFM, Silva NSB, Castro CFB, Andrade HS, Souza AS, et al. A large familial cluster and sporadic cases of frontal fibrosing alopecia in Brazil reinforce known human leucocyte antigen (HLA) associations and indicate new HLA susceptibility haplotypes. J Eur Acad Dermatol Venereol 2020;34:2409–13.

Ramot Y, Bertolini M, Boboljova M, Uchida Y, Paus R. PPAR-γ signalling as a key mediator of human hair follicle physiology and pathology. Exp Dermatol 2020;29:312–21.

Ramot Y, Böhm M, Paus R. Translational neuroendocrinology of human skin: concepts and perspectives. Trends Mol Med 2021;27:60–74.

Ramot Y, Mastrofrancesco A, Herczeg-Lisztes E, Bíró T, Picardo M, Kloepper JE, et al. Advanced inhibition of undesired human hair growth by PPARγ modulation? J Invest Dermatol 2014;134:1128–31.

Ranasinghe GC, Piliang MP, Bergfeld WF. Prevalence of hormonal and endocrine dysfunction in patients with lichen planopilaris (LPP): a retrospective data analysis of 168 patients. J Am Acad Dermatol 2017;76: 314–20.

Rigopoulos D, Stamatios G, Ioannides D. Primary scarring alopecias. Curr Probl Dermatol 2015;47:76–86.

Rivas MMO, Antolín SC, Sambucety PS, González ES, Ruíz de Morales JMG, Prieto MÁR. Frontal fibrosing alopecia and lichen planopilaris in HLA-identical mother and daughter. Indian J Dermatol Venereol Leprol 2015;81:162–5.

Rocha VB, Donati A, Contin LA, Kakizaki P, Machado CJ, Brito FF, et al. Photopatch and patch testing in 63 patients with frontal fibrosing alopecia: a case series. Br J Dermatol 2018;179:1402–3.

Rocha VB, Pires MC, Contin LA. Familial fibrosing frontal alopecia in six sisters. An Bras Dermatol 2020;95:125–8.

Rosenblum MD, Olasz EB, Yancey KB, Woodliff JE, Lazarova Z, Gerber KA, et al. Expression of CD200 on epithelial cells of the murine hair follicle: a role in tissue-specific immune tolerance? J Invest Dermatol 2004;123:880–7.

Salas-Callo CI, Cajas-García MS, Pirmez R. Hypopigmentation of the eyebrows in frontal fibrosing alopecia. Skin Appendage Disord 2021;7:243–5.

Samuelov L, Sprecher E, Tsuruta D, Bíró T, Kloepper JE, Paus R. P-cadherin regulates human hair growth and cycling via canonical Wnt signaling and transforming growth factor-β2. J Invest Dermatol 2012;132:2332–41.

Sawaya AP, Jozic I, Stone RC, Pastar I, Egger AN, Stojadinovic O, et al. Mevastatin promotes healing by targeting caveolin-1 to restore EGFR signaling. JCI Insight 2019;4:e129320.

Słoniecka M, Danielson P. Substance P induces fibrotic changes through activation of the RhoA/ROCK pathway in an in vitro human corneal fibrosis model. J Mol Med (Berl) 2019;97:1477–89.

Stang E, Kartenbeck J, Parton RG. Major histocompatibility complex class I molecules mediate association of SV40 with caveolae. Mol Biol Cell 1997;8:47–57.

Stefanato CM. Histopathology of alopecia: a clinicopathological approach to diagnosis. Histopathology 2010;56:24–38.

Strazzulla LC, Avila L, Lo Sicco K, Shapiro J. Response to "Frontal fibrosing alopecia in men: an association with facial moisturizers and sunscreens.". Br J Dermatol 2017;177:323.

Sugawara K, Bíró T, Tsuruta D, Tóth BI, Kromminga A, Zákány N, et al. Endocannabinoids limit excessive mast cell maturation and activation in human skin. J Allergy Clin Immunol 2012;129:726–38.e8.

Tavakolpour S, Mahmoudi H, Abedini R, Kamyab Hesari K, Kiani A, Daneshpazhooh M. Frontal fibrosing alopecia: an update on the hypothesis of pathogenesis and treatment. Int J Womens Dermatol 2019;5:116–23.

Tiede S, Hundt JE, Paus R. UDP-GlcNAc-1-Phosphotransferase is a clinically important regulator of human and mouse hair pigmentation. J Invest Dermatol 2021;141:2957–65.e5.

Tomassian T, Humphries LA, Liu SD, Silva O, Brooks DG, Miceli MC. Caveolin-1 orchestrates TCR synaptic polarity, signal specificity, and function in CD8 T cells. J Immunol 2011;187:2993–3002.

Tron VA, Coughlin MD, Jang DE, Stanisz J, Sauder DN. Expression and modulation of nerve growth factor in murine keratinocytes (PAM 212). J Clin Invest 1990;85:1085–9.

Tziotzios C, Fenton DA, Stefanato CM, McGrath JA. Familial frontal fibrosing alopecia. J Am Acad Dermatol 2015;73:e37.

Tziotzios C, Petridis C, Dand N, Ainali C, Saklatvala JR, Pullabhatla V, et al. Genome-wide association study in frontal fibrosing alopecia identifies four susceptibility loci including HLA-B*07:02. Nat Commun 2019;10:1150.

Tziotzios C, Stefanato CM, Fenton DA, Simpson MA, McGrath JA. Frontal fibrosing alopecia: reflections and hypotheses on aetiology and pathogenesis. Exp Dermatol 2016;25:847–52.

Uchida Y, Gherardini J, Pappelbaum K, Chéret J, Schulte-Mecklenbeck A, Gross CC, et al. Resident human dermal γδT-cells operate as stress-sentinels: lessons from the hair follicle. J Autoimmun 2021;124:102711.

Uchida Y, Gherardini J, Schulte-Mecklenbeck A, Alam M, Chéret J, Rossi A, et al. Pro-inflammatory Vδ1+T-cells infiltrates are present in and around the hair bulbs of non-lesional and lesional alopecia areata hair follicles. J Dermatol Sci 2020;100:129–38.

Vadevoo SMP, Gunassekaran GR, Lee C, Lee N, Lee J, Chae S, et al. The macrophage odorant receptor Olfr78 mediates the lactate-induced M2 phenotype of tumor-associated macrophages. Proc Natl Acad Sci USA 2021;118:e2102434118.

Vañó-Galván S, Molina-Ruiz AM, Serrano-Falcón C, Arias-Santiago S, Rodrigues-Barata AR, Garnacho-Saucedo G, et al. Frontal fibrosing alopecia: a multicenter review of 355 patients. J Am Acad Dermatol 2014;70:670–8.

Vañó-Galván S, Saceda-Corralo D, Alonso-Castro L, Urech M, Espada J. Antiandrogenic drugs, a therapeutic option for frontal fibrosing alopecia patients [published correction appears in J Am Acad Dermatol 2018;78:431]. J Am Acad Dermatol 2016;74:e77.

Vañó-Galván S, Saceda-Corralo D, Blume-Peytavi U, Cucchía J, Dlova NC, Gavazzoni Dias MFR, et al. Frequency of the types of alopecia at twenty-two specialist hair clinics: A multicenter study. Skin Appendage Disord 2019a;5:309–15.

Vañó-Galván S, Trindade de Carvalho L, Saceda-Corralo D, Rodrigues-Barata R, Kerkemeyer KL, Sinclair RD, et al. Oral minoxidil improves background hair thickness in lichen planopilaris. J Am Acad Dermatol 2021;84:1684–6.

Vañó-Galván S, Villodres E, Pigem R, Navarro-Belmonte MR, Asín-Llorca M, Meyer-González T, et al. Hair transplant in frontal fibrosing alopecia: a multicenter review of 51 patients. J Am Acad Dermatol 2019b;81:865–6.

Villani A, Fabbrocini G, Ocampo-Candiani J, Ruggiero A, Ocampo-Garza SS. Review of oral minoxidil as treatment of hair disorders: in search of the perfect dose. J Eur Acad Dermatol Venereol 2021;35:1485–92.

Wilk M, Zelger BG, Zelger B. Lichen planopilaris-histologic criteria and clues in vertical sections. Hair Ther Transplant 2013;3:1.

Wong D, Goldberg LJ. The depth of inflammation in frontal fibrosing alopecia and lichen planopilaris: a potential distinguishing feature. J Am Acad Dermatol 2017;76:1183–4.

Zhang B, Ma S, Rachmin I, He M, Baral P, Choi S, et al. Hyperactivation of sympathetic nerves drives depletion of melanocyte stem cells. Nature 2020;577:676–81.