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. 

Cited article as: JID Innovations 2022;2:100113 doi:10.1016/j.xjidi.2022.100113

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Abbreviations: 5ARI, 5α-reductase inhibitor; 8-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; MHC, macrophage; MHCII, major histocompatibility complex; PCA, primary cicatricial alopecia; PCP, personal care product; PPAR-γ, peroxisome proliferator–activated receptor-γ; SC, stem cell; SP, substance P

Received 8 October 2021; revised 21 January 2022; accepted 26 January 2022; accepted XXX; corrected proof published online XXX

Cite this article as: JID Innovations 2022;2:100113

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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

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**Table 1. Clinical and Immunohistopathological Characteristics of FFA and LPP**

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

Abbreviations: DIF, direct immunofluorescence; 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.
Fronto-temporal recession with band-like atrophic skin, loss of eyebrows, facial papules, perifollicular erythema, and lonely hairs.

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.

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 HFVs 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. (2021)) of the key processes involved in LPP and FFA development from healthy HFVs until the occurrence of permanent scarring alopecia. We showed the progression of healthy HFVs possessing some predisposing factors (in blue). When these predisposed HFVs 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 HFVs 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; Vanó-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 HFVs [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 HFVs show loss of melanocytes [Lin et al., 2017; Salas-Calio 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 reversibly 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 HFVs (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 HFVs 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 fetoepitheloblast, 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 Vδ1+ 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 (Doché 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 (Cheret 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 and, 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: two 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; Porrino-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 our 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; Keremeyer 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 and to which extent the factors discussed in the following sections and listed in Table 2 exert and possibly coalesce in

### 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) | Diegen 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%                        | 8.1%                            | 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%                           |                               |
| MU/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; MU/MCI, methylisothiazolinone/methylchloroisothiazolinone.

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; Vaño-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
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 PubMed analysis trends have been used by authors to show the increase in FFA numbers by reporting the surge in FFA through 1994 and 2021, respectively, compared with 1 and 9 total articles published 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 the 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%) (Vahé-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-cleanness.

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 one way or another. Certain 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-cleanness.

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 z-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 enhance 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 (Migliio 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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