Frontiers in Lichen Planopilaris and Frontal Fibrosing Alopecia Research:

Pathobiology Progress and Translational Horizons

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ABSTRACT

Lichen planopilaris (LPP) and frontal fibrosing alopecia (FFA) are primary, lymphocytic cicatricial hair loss disorders. These model epithelial stem cell diseases are thought to result from a CD8+ T cell-dominated immune attack on the hair follicle’s stem cell niche (bulge) after the latter has lost its immune privilege for as yet unknown reasons. This induces both apoptosis and pathological epithelial-mesenchymal transition (EMT) in epithelial stem cells, thus depletes the bulge, causes fibrosis, and ultimately abrogates hair follicle’s capacity to regenerate. Here, 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 towards direly needed progress in the management of these disfiguring, deeply distressful cicatricial alopecia variants, we advocate to focus on the development of bulge immune privilege and epithelial stem cell protectants such as, for example, topically effective, *hair follicle-penetrating* and immunoinhibitory preparations that contain tacrolimus, PPARg and/or cannabinoid receptor-1 agonists.
THE CHALLENGE

Lichen planopilaris (LPP) and frontal fibrosing alopecia (FFA) are inflammatory scarring hair loss disorders that primarily affect peri- and post-menopausal women. These primary cicatricial alopecias (PCA) result in disfiguring hair loss, significant scalp symptoms, secondary cutaneous morbidity, (Fertig et al. 2018), severely reduced quality of life (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 upon 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; 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 demographic and ethnic distribution within defined populations; reliable and predictive biomarkers of disease activity, course, and therapeutic response; genetic, environmental, microbial, cosmetic and nutritional factors at play in both populations and individuals that are a) shared between and b) 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 - as 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 towards 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, Figure 1a and b) and (immune-)histopathology (Table 1, Figure 2a and b). These table and figures demonstrate the histopathological similarity of both PCAs, in striking contrast to their very distinct clinical phenotypes (though overlap variants do exist [Du et al. 2020; Griggs et al. 2020; Rigopoulos et al. 2015; Vañó-Galván et al. 2019]). 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 disease

Specifically, we need to ask whether LPP and FFA are primarily regional (“territorial”) diseases dominated by localized epithelial hair follicle (HF) stem cell 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, since the former implies that optimal disease management primarily demands early and decisive intervention at the local skin level, while 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 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.

Based on recent studies and as depicted in **Figure 3A**, intracutaneous pathobiology elements and **locally active** environmental factors seem to be key factors in the development of both LPP and FFA (Chiang et al. 2015; Chiang et al. 2012; Harries et al. 2020; Harries et al. 2018). Such environmental factors may 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 induces neurogenic inflammation and immune privilege collapse of human scalp HFs (Peters et al. 2007) while noradrenaline can induce proliferation and thus exhaustion of HF melanocytes stem cells 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 hotly 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. 2020), 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 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)).

What remains painfully unclear in this scenario though is the initiating, primary factor(s) that render(s) the bulge of previously healthy or non-lesional HFs (in LPP/FFA-affected patients) susceptible to immune privilege collapse and/or epithelial stem cell apoptosis and EMT (see below). While PPARg dysfunction and a dysregulation of PPARg-stimulating lipid mediators has been postulated as such a primary factor (Karnik et al. 2009). PPARg-signaling is indeed an important regulator of human HF physiology and a major epithelial stem cell protectant (see 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 PPARg expression does not differ substantially between lesional and non-lesional HFs of patients affected by LPP/FFA (Harries et al. 2013). This questions whether, but does not rule out that, insufficient PPARg-mediated signaling really initiates LPP/FFA pathogenesis.

The most important genetic FFA study published so far has identified several genes to be associated with FFA while some others were overexpressed in full thickness lesional skin biopsies (see below) (Tziotzios et al. 2019). Yet, the functional relevance of none of the identified genes has as yet been 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, HF microbiome-related factors and/or leave-on cosmetics (Harries et al. 2018).

**Epithelial stem cell niche immunopathology: the bulge immune privilege collapse concept**

All currently available evidence suggests that LPP and FFA both result from immune targeting and eventually depletion of the HF’s epithelial stem cell (eHFSC) reservoir, which ultimately exhausts the HF’s ability to regenerate and causes loss of HFs. These eHFSCs are located inside the bulge epithelium, a hair follicle compartment that exhibits the classical immune phenotype a tissue niche that has established a relative immune privilege (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 down-regulation of MHC class I and β2-microglobulin (β2MG) molecules and by the creation of an immuno-inhibitory environment generated by IP “guardians” such as IL-10, TGFβ1, TGFβ2, α-MSH and IGF-1 (Bertolini et al. 2020; Ito et al. 2004b; Paus et al. 2005).

Just as in alopecia areata, where the disease cannot develop without collapse of the IP of the anagen hair bulb having occurred (Gilhar et al. 2019; Gilhar et al. 2012), the collapse of bulge IP may be an essential first step in the pathogenesis of LPP and FFA (Harries et al. 2013). As yet, no lesional LPP or FFA HFs have been identified that lack bulge IP collapse when the latter was examined. Moreover, selectively deleting in mice the “no danger” signal, CD200, a key element of bulge IP (Meyer et al. 2008; Ohyama et al. 2006), in K15+ eHFSCs induces a murine PCA phenotype that displays 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, IFNγ, 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.

What remains quite unclear to-date though 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. While the bulge gene and protein expression profile of established lesional versus non-lesional bulge regions in both LPP and FFA patients is characterized by an upregulation of transcriptional markers of IFNγ-related signaling (Harries et al. 2013), this does not yet prove that excessive IFNγ secretion is indeed the proverbial “match that lights the fire”. Yet, IFNγ currently is the best candidate to fit this bill – not the least since IFNγ-secreting cytotoxic, perforin+ CD8+ T cells seem to be the first immunocytes that can be identified on the crime scene, i.e. inside the bulge epithelium of lesional LPP or FFA HFs; also, other immunocytes involved in immune-mediated damage of the bulge region, such as CXCR3+ (Harries et al. 2020; Harries et al. 2013) and FOXP3+ T cells also prominently secrete IFNγ (Harries et al. 2020).

Nevertheless, other players that have surfaced in the context of alopecia areata research might induce bulge IP collapse, as well. These include the neuropeptide, substance P, 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 below), and possibly also IL-12, which can induce human hair bulb IP collapse (Edelkamp et al, 2021 EADV abstract in press). Also, human HFs are
constantly being “policed” by γδT cells, namely by Vδ1+ T lymphocytes, which can recognize markers of tissue distress such as MICA protein expression via their NKG2D receptors; activation of the latter induces IFNγ secretion by these cells, followed by IP collapse in the anagen hair bulb (Uchida et al. 2021; Uchida et al. 2020). NKG2D+ NK cells can exert very similar functions and thereby induce alopecia areata 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 IFNγ-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 below], or non-specific danger signals like 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, e.g. by cytotoxic, perforin+ 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 frustrate damage-repair attempt?) while the apoptotic cell machinery has already been activated, thus further expediting 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”, i.e. IFNg and perforin (Harries et al. 2018; Harries et al. 2013).

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

Human eHFSCs seem to have yet another Achilles heel: their vulnerability to undergo pathological epithelial-mesenchymal transition (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, since as 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 up-regulation 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 epithelium 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, TGFß1, and IFNg) 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 IFNg secretion, but on the other 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, 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, while 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 initial shared pathobiology events (i.e. bulge IP collapse, eHFSC apoptosis and EMT) have 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 below), while
pathogenic activities of peri-bulge macrophages might promote 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

While reported pediatric cases of LPP are rare, they outnumber the even rarer reported pediatric cases of FFA (>12:3). There are only 3 reports of pediatric FFA in the literature: 14-year-old twin sisters who developed FFA at 5 years of age, and a 7-year-old female with FFA (Atarguine et al. 2016). While the histology of the 7-year-old female 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 “a depletion of hair follicles 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 that is further supported by the recent Tziotzios et al. (Tziotzios et al. 2019) 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 6 sisters (Rocha et al. 2020), and at least 7 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 5 out of 7 sporadic cases that they included as well (Ramos et al. 2020). Specifically in the familial cluster of FFA cases in this study, 3 out of 4 unaffected family members had these alleles present, suggesting a role for 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 towards 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 LPP patients had a significantly higher frequency of the DRB1*11 and DQB1*03 alleles compared to controls (Pavlovsky et al. 2015). DQB1*03 has been implicated as a susceptibility locus for alopecia areata (AA) and in IP collapse. In yet another study of LPP patients, 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 upon 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 aryl hydrocarbon receptor (AhR), a cellular receptor that plays a role in 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 as compared to controls, and 30% of LPP and FFA patients had increased expression of AhR+ cells on the affected scalp compared to the unaffected area (Doche et al. 2020a). A genome-wide association study (GWAS) and meta-analysis in female FFA patients 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, since 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 (Figure 3a: “trunk”) and diverge (Figure 3b: LPP vs. FAA “branch”). Also unclear is the pathobiological relevance of the haplotypes and the candidate genes. No functional confirmation, e.g. via 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 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 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 below and listed in Table 2 exert, and possibly coalesce in, any epigenetic changes that impact on 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 stem 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 androgenic alopecia (AGA) that occurs in patients with LPP and FFA have led some authors to propose a role for androgen excess in FFA, based largely upon the post-menopausal predominance of affected females (Dawn et al. 2003; Ranasinghe et al. 2017). While definitive evidence for this hypothesis is missing, reports of clinical benefits seen in some patients treated with 5alpha reductase inhibitors such as dutasteride (Jerjen et al. 2021; Lobato-Berezo et al.
2018; Panchapranteep et al. 2020; Pindado-Ortega et al. 2021; Vañó-Galván et al. 2016) (Pindado-Ortega et al. 2021), have been interpreted as supporting it. However, retrospective cohort studies of moderate quality where patients were treated with concomitant therapies in addition to 5ARIs, and/or serum androgen and estogens 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 due 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. 69% of the subjects were post-menopausal, and 31% had a history of polycystic ovary syndrome (PCOS). 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 LPP patients and 35.6% of LPP/FFA patients but, surprisingly, not in the FFA only group; in contrast, androgen deficiency was seen in 32.1% of FFA patients (Ranasinghe et al. 2017). In a cross-sectional study of 711 female FFA patients, 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 post-menopausal 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 34-year-old male lithographer exposed to occupational chlorinated hydrocarbons, heavy metals, and strong acids (Macleod 1909). Later, another report of sudden eruption of follicular inflammatory lesions on the abdomen which quickly generalized to involve the scalp was reported in a 43-year-old female just one month after undergoing a dilatation and curettage for menorrhagia (Peters 1939). Perhaps most striking is a recent case of a 35-year-old male construction worker who acutely developed biopsy-proven LPP two weeks after high-concentration exposure to trichloroethylene (TCE) and perchloroethylene (PCE) 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 raises 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 due to the distribution of hair loss being in areas of frequent contact with personal care products (moisturizers, cosmetics) and sunscreens. PubMed analysis trends have been used by authors to demonstrate 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 to 1 and 633 articles published on FFA over this same time course. Notably, a 2019 multi-center study of specialty alopecia clinics across 4 continents reported that the frequency of FFA patients was 10.8% followed closely by LPP (7.6%) (Vañó-Galván et al. 2019a). While 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 hair care products to the US Food and Drug Administration (FDA), with above average reports of serious health outcomes associated with items used for personal cleanliness hair care and hair coloring products (Kwa et al. 2017). Further, three hair product lines have been subjects of class action lawsuits in the US, namely Brazilian Blowout, Chaz Dean’s Wen products, and DevaCurl, with consumers reporting hair loss and scalp inflammation after use of these products (Nutrition 2020). While 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.

**Personal Care Products**

The increase in cases of FFA, the distribution of involvement, and that it largely affects post-menopausal women has stimulated research into the possibility that personal care products (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 FFA patients 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). While these studies did not include patients with LPP, another patch testing study of 42 LPP and FFA patients reported that 76% had at least one, relevant positive allergic reaction to ingredients in their personal care products (PCPs) used on the head and neck (Prasad et al. 2020). There were no differences in rates of allergy between patients with LPP and 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 rates of allergy compare to 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 to 14.3%, 10%, 5%, and 8.3% reported in the LPP and FFA population (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 hair follicle 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 (ORs), and whose stimulation both, regulates hair growth (Chéret et al. 2018) and can impact on tissue pathology in various systems (Maßberg and Hatt 2018). OR stimulation with a synthetic odorant contained in many perfumes and after-shaves also stimulates the production of potent antimicrobial peptides in human scalp HFs ex vivo (Chéret et al. 2018) and thus may impact on the composition of the HF microbiome (Lousada et al. 2020). ORs are expressed by many immune cell populations including CD8+ T cells and macrophages (MACs) (Clark et al. 2016), and activation of specific MAC surface ORs can induce chemokine secretion (Li et al. 2013) and polarization into M2 macrophages (Vadevoo et al. 2021). This is interesting, since the M2 phenotype is preferentially increased around lesional LPP HFs (Fig. 2a, (Harries et al. 2020), raising the question whether this or other ORs might be involved in the development of LPP.

Recently, we found that LPP patients 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. 2016), another key site of immune privilege like the HF bulge. Therefore, the potential role of odorant-induced, OR-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 for in future LPP/FFA management. The scaffolding protein, caveolin-1 (Cav1), a key structural component of caveolae, not only co-localizes with
keratin 15 in the outer root sheath and eHFSCs of human scalp HFs, but its expression is also significantly elevated in lesional FFA compared to healthy scalp HFs (Jozic et al. 2021b). Furthermore, it is well-established that Cav1 inhibits TGF-β- 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 expression of IFNγ, the key inducer of bulge HF IP collapse, as well as substance P and MICA (Oakley et al. 2009; Stang et al. 1997; Tomassian et al. 2011) (Oakley et al. 2009; Stang et al. 1997; Tomassian et al. 2011). Moreover, the substance P receptor, neurokinin (NK1), localizes to caveolae, and disruption of caveolae by cholesterol depleting agents significantly reduces substance P reactivity and activation of NK1 receptor in mice (Monastyrskaya et al. 2005). Additional arguments in support of elucidating the role of caveolins and caveoale 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), that overexpression of Cav1 can lead to downregulation of E-cadherin and an upregulation of vimentin (Cokakli et al. 2009) and thus promotes EMT. Thus, pharmacologically down-regulating caveolins might help to protect the bulge from both, IP collapse and pathological EMT (Jozic et al. 2021b).

**Dysbiosis**

There is increasing interest in the role of HF dysbiosis in various hair diseases, such as alopecia areata and androgenetic alopecia, while very little is as yet known about the HF microbiome in LPP and FFA (Constantinou et al. 2021b; Constantinou et al. 2021a; Hisham Diab Gaber et al. 2015; Lousada et al. 2020; Pinto et al. 2019; Polak-Witka et al. 2020). Since *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 impact of bacterial colonization and HF dysbiosis also LPP and FFA.

Interestingly, in female LPP and FFA patients *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 FFA and LPP patients compared to healthy controls while 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 to healthy controls, suggesting a role for imbalance between these bacterial species in the development of these PCAs (Constantinou et al. 2021b). This was accompanied by a strong upregulation of both beta defensin 1 and 2 in LPP and FFA patients (these beta-defensins are well known T cell attractants (Kanda et al. 2011; Niyonsaba et al. 2004)). Dissecting the role of HF dysbiosis and related abnormalities in chemokine secretion, bulge expression of “danger signals” like MICA, and changes in the local production of pro-inflammatory antimicrobial peptides in the early stages of LPP/FFA pathogenesis, thus, promises to be a particularly fertile and translationally relevant research frontier.

**Stress and neurogenic inflammation**

While our understanding of how psychological stress and hair loss might be related is still quite incomplete (Paus and Arck 2009), human HF exhibit a fully functional, local hypothalamic-pituitary-adrenal axis (HPA) 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 substance P (SP) receptor, NK1 (Arck et al. 2005; Arck et al. 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 growth factor 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 p75NTR (Peters et al. 2007), whose activation by NGF triggers apoptosis of HF keratinocytes; SP also stimulates TNFα release, which further promotes HF keratinocyte 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 macrophages in human skin (Gherardini et al. 2020), whose number is significantly increased around the bulge of LPP, notably more so than around FFA-affected scalp HFs (Figure 2A, (Harries et al. 2020)). Therefore, SP-dependent neurogenic (stress-induced?) peri-bulbar inflammation could also play a role in triggering and/or aggravating LPP and FFA pathobiology; however, this remains to be conclusively demonstrated.

**FUTURE DIRECTIONS AND THERAPEUTIC INTERVENTIONS**

Based on 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. Since FK 506 both prevents experimentally induced IP collapse in the human anagen hair bulb and promotes HF IP restoration \textit{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 is already has some therapeutic benefit in selected patients with FFA or LPP (Blazek and Megahed 2008; Giorgio et al. 2021; Mahmoudi et al. 2020), strongly encourages one to pursue HF-targeting vehicle development for this drug and other candidate bulge IP guardians, such as extended-activity aMSH (afamelanotide) (Ito et al. 2004b) that might be repurposed for topical LPP/FFA treatment.

Given the potential role of substance P and NK1 in peri-bulge neurogenic inflammation, it also deserves to be tested whether clinically available NK1 antagonists like 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., via cyclodextrins/statins) (Jozic et al. 2021a; Jozic et al. 2019; Sawaya et al. 2019) or by nanoparticle-mediated siRNA delivery, can halt the - often relentless – progression of FFA/LPP and can be used as auxiliary therapy to the other candidate therapeutics discussed here. Interestingly, the OR2AT4 agonist, Sandalore, which prolongs anagen \textit{ex vivo} (Chéret et al. 2018), also downregulates expression of Cav1 at both mRNA and protein levels.
(Chéret et al. 2020; Jozic et al. 2021b). Besides targeting caveolin-1 therapeutically, it may also be an overlooked candidate biomarker of disease progression and activity (Jozic et al. 2021b).

The PPARγ modulator, NAGED, not only prevents and partially reverses experimentally induced EMT in the human bulge (Imanishi et al. 2018) and up-regulates keratin 15 expression in eHFSCs ex vivo (Ramot et al. 2014), but also protects keratin 15+ 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 downregulation of the key mitochondrial transcription factor A (TFAM) (Hardman-Smart et al. 2020). Since TFAM is upregulated by PPARγ (Miglio et al. 2009), PPARγ 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 OR-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 macrophage and dendritic cell activities at the level of the bulge and/or alter the physiological composition of the HF microbiome via OR-controlled changes in the intrafollicular production of antimicrobial peptides (Chéret et al. 2018).

Importantly, directions for future research must investigate genetic and pathogenic mechanisms of LPP, FFA, and LPP/FFA overlap in tandem, as 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 LPP and/or FFA patients who provide such research samples, including the degree of severity and disease activity, will provide important information to help guide 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 demonstrates that refocusing the attention on the pathobiology of LPP and FFA along with the system of coordinates delineated and the specific suggestions made here has a real translational value. Indeed, it promises to both, greatly accelerate the development of long-awaited much more effective LPP/FFA therapies, and to supply us with robust molecular biomarkers of disease and therapy response.

Data Availability Statement: No datasets were generated or analyzed during the current study.

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Conflicts of interest: For the record, RP is CEO of a skin and hair research company (www.monasteriumlab.com) that has performed contract research on the impact of PPARg and olfactory receptor ligands on human hair follicles, but holds no patents and does not develop products in this area. All other authors declare not conflict of interest.

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Writing – original draft: MMS and RP, Writing – review & editing: EP, JC, and IJ.

Visualization: MMS, RP, EP, JC, and IJ.
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<table>
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<th>Distinct Histopathological Characteristics*</th>
<th>Shared Histopathological Characteristics</th>
<th>Distinct Clinical Characteristics</th>
<th>Shared Clinical Characteristics</th>
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</thead>
</table>
| Lichen Planopilaris | - more severe inflammatory infiltrate and less apoptosis.\(^4,7\)  
- concentric lamellar fibroplasia\(^7\)  
- more basilar layer and interfollicular epidermal damage.\(^4\)  
- increased melanocyte counts in the upper hair follicle.\(^10\)  
- DIF demonstrates less IgM immunofluorescence and IgG, IgA and IgM in papillary dermis.\(^9\)  
- increased CD68+ macrophage polarization and upregulated CD163 and IL4.\(^11\) | - lichenoid perifollicular lymphocytic infiltration (most evident in superior aspects of the hair follicle)\(^1,2\)  
- infundibular hyperkeratosis and hypergranulosis.  
- hair epithelium demonstrates vacuolar degeneration, necrotic keratinocytes, and perifollicular loss of elastin fibers with fibrosis.\(^12\)  
- superficial pigment incontinence.\(^3,13\)  
- follicular plugging, epidermal/dermal clefts, sebaceous gland destruction.\(^5\)  
- chronic stage demonstrates dilated blood vessels and band-like vertical scarring beneath papillary dermis.\(^5\)  
- late stage demonstrates extensive perifollicular lamellar fibrosis surrounding the infundibulum.\(^5\)  
- similar expression profiles of CD1a, CD3, CD4, CD8, CD68, and IDO in immunohistochemical studies.\(^9\)  
- increased CD8+, CXCR3+, FOXP3+ T cells and CD68+ macrophages.\(^11\)  
- increased total and degranulated mast cells and CD123+ dendritic cells.\(^11\) | - asymmetric multifocal involvement of scarring alopecia.\(^13\)  
- perifollicular erythema and keratotic follicular papules.\(^13\)  
- most commonly vertex and parietal scalp, but all regions can be involved.\(^2\)  
- association with oral, ungual, or cutaneous lichen planus.\(^13\)  
- dermoscopy demonstrates: elongated concentric blood vessels, violaceous-blue interfollicular areas, big irregular white dots.\(^13\) | - dermoscopy demonstrates: loss of follicular ostia, peripilar white scales and peripilar erythema.\(^13\)  
- symptoms of pruritus, pain, and burning.\(^14\) |
| Frontal Fibrosing Alopecia | - extension of the inflammatory infiltrate below the isthmus.\(^6\)  
- islands of sparing of interfollicular epidermis\(^8\)  
- less prominent inflammatory infiltrate, with more numerous necrotic keratinocytes and foreign body reaction.\(^4\)  
- more frequent terminal catagen-telogen hairs.\(^7\)  
- DIF demonstrates cytoid bodies of IgM in the papillary dermis and epidermal and follicular basement membrane zones.\(^9\) | - - symmetric, progressive frontotemporal hairline recession in a “a band-like” pattern above the patient’s normally pigmented and wrinkled forehead.  
- less frequent recession of pre- and postauricular areas and occipital scalp.  
- dermoscopy demonstrates: peripilar white scales and erythema, regularly distributed red or grey dots in eyebrows, peripilar erythema\(^13\)  
- skin-colored facial papules.  
- marked or complete loss of eyebrows, typically beginning laterally.\(^13\) |
- increased Langerhans cells in the infundibuloisthmic region compared to LPP.\textsuperscript{12}  
- decreased numbers of of CD1a+ and CD209+ dendritic cells in the infundibulum connective tissue sheath.\textsuperscript{11}  
- general thinning of the beard and peripheral body hair.  
- absence of vellus hair in the hairline.

*While 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.

**Table I. Clinical and Immuno-Histopathological Characteristics of FFA and LPP**

**References:**

Table 2: Frequency of positive patch test results in patients with LPP and/or FFA compared to rates in the European general population.

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Prasaad et al (n=42)</th>
<th>Aldoori et al (n=40)</th>
<th>Rocha et al (n=63)</th>
<th>Pastor-Nieto et al (n=36)</th>
<th>Diepgen et al (n=3119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of patients with at least one positive relevant allergen</td>
<td>76%</td>
<td>52.5%</td>
<td>27%</td>
<td>80.5%</td>
<td>27%</td>
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<tr>
<td>Gallates</td>
<td>26.2%</td>
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<tr>
<td>Fragrance Mix I</td>
<td>14.3%</td>
<td>10.0%</td>
<td>5.0%</td>
<td>8.3%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Linalool</td>
<td>19.0%</td>
<td>22.5%</td>
<td>8.0%</td>
<td>5.5%</td>
<td></td>
</tr>
<tr>
<td>Limonene</td>
<td>4.8%</td>
<td></td>
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<tr>
<td>Ammonium persulfate</td>
<td>14.3%</td>
<td></td>
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<td></td>
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<tr>
<td>Benzophenone 4</td>
<td>14.3%</td>
<td>12.5%</td>
<td>8.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzyl salicylate</td>
<td>4.8%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Propolis</td>
<td>9.5%</td>
<td></td>
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<tr>
<td>MI/MCI*</td>
<td>11.9%</td>
<td>17.5%</td>
<td>2.8%</td>
<td>0.5%</td>
<td></td>
</tr>
<tr>
<td>Balsam of Peru</td>
<td>7.1%</td>
<td>12.5%</td>
<td>8.0%</td>
<td>5.5%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

* Methylchloroisothiazolinone/Methylisothiazolinone

References:


FIGURE LEGENDS

**Figure 1. Clinical Characteristics of LPP and FFA**

Macroscopic and dermatoscopic views of biopsy proven frontal fibrosing alopecia (a) and lichen planopilaris (b), demonstrating key clinical characteristics features. All subjects consented to the publication of the images.

**Figure 2. Immunohistopathologic Characteristics of LPP and FFA**

a.1. Quantitative display of median cell counts for all statistically significant results of CD68+ macrophages in key parts of follicular anatomy involved in lichen planopilaris (LPP), frontal fibrosing alopecia (FFA), and control groups (Harries et al. 2020).

a.2. Photographic images of CD68 positivity at the hair follicle bulge region in lichen planopilaris (LPP) and frontal fibrosing alopecia (FFA). APM, arrector pili muscle (Harries et al. 2020).

a.3. CD68 macrophage M1 marker is downregulated and M2 marker CD163 is upregulated in lesional lichen planopilaris (LPP) skin compared with nonlesional LPP and frontal fibrosing alopecia (FFA). The percentages of macrophages (CD68+) expressing each marker in the connective tissue sheath (CTS) were calculated and expressed as the fold change calculated from patient-matched nonlesional skin (Harries et al. 2020).

b.1,2,3. H&E staining demonstrating key similarities of histopathology samples of LPP and FFA (Chiang et al. 2012).
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 and immune privilege collapse, EMT but also additional pathways more recently identified like 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, 2021) of key processes involved in LPP and FFA development from healthy until 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. Abbreviations: HF: hair follicle; EMT, epithelial–mesenchymal transition; IP: immune privilege; FFA, frontal fibrosing alopecia; LPP, lichen planopilaris; PPAR-γ, peroxisome proliferator-activated receptor-γ; CYP1A1: Cytochrome P450, family 1, subfamily A, polypeptide 1; FOXP3: Forkhead box protein P3.
a) Biopsy proven Frontal fibrosing alopecia

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

b) Biopsy proven Lichen Planopilaris

Asymmetric, multifocal, alopecia of vertex and parietal scalp. Perifollicular erythema and keratotic follicular papules.
3. Downregulation of macrophage M1 marker CD86 vs M2 marker CD163 upregulation in LPP vs FFA.

Figure 2. Immunohistopathologic Characteristics of LPP and FFA

a. Distinct Features

1. Statistically significant differences in CD68+ macrophage expression in patients with lichen planopilaris (LPP), frontal fibrosing alopecia (FFA) and controls.

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

b. Shared Features

1. Lichenoid, perifollicular lymphocytic infiltrate.

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

3. (a) perifollicular inflammation and interface change localized to the infundibulum.
   (b) squamatization of the basal follicular epithelium, perifollicular fibrosis and inflammation.
Proposed predisposing factors:
- PPARg deficiency
- Disrupted lipid synthesis

Proposed amplifying factors:
- EMT
- Immune cells recruitment
- Microbial infection + antimicrobial peptides secretion
- Cell apoptosis
- Environmental factors

LPP development

FFA development