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Review Article

Advancements in Research on Lichen Planopilaris and Frontal Fibrosing Alopecia: Exploring Pathobiological Developments and Translational Prospects

Madeha Al-Kelani*, Kutlwano Molema and Sincengile Ntshingila
Hair and Skin Research Laboratory, Division of Dermatology, Department of Medicine Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory, Cape Town, South Africa.

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***Corresponding author:** Madeha Al-Kelani, Hair and Skin Research Laboratory, Division of Dermatology, Department of Medicine Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory, Cape Town, South Africa.

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Abstract:

Frontal fibrosing alopecia (FFA) and lichen planopilaris (LPP) are primary lymphocytic hair loss disorders predominantly affecting perimenopausal and postmenopausal women. FFA is often regarded as a variant of LPP due to similar histological findings, including perifollicular lymphohistiocytic infiltrate with a lichenoid pattern. Despite an increase in the prevalence of FFA and LPP over the past decade, their etiology and pathophysiology remain unclear.

This review highlights recent findings on the pathogenesis of FFA and LPP, focusing on immunomodulation, neurogenic inflammation, and genetic factors. A prolonged inflammatory response and collapse of immune privilege trigger the loss of epithelial hair follicle stem cells (eHFSCs) and epithelial-mesenchymal transition (EMT), leading to the replacement of healthy hair follicles with fibrous tissue. Familial reports and genome-wide association studies suggest a genetic or epigenetic basis for FFA development.

Current therapeutic options are limited, underscoring the need for further research and cohort studies to elucidate the etiology and improve treatment strategies for these conditions.

Keywords: frontal fibrosing alopecia; lichen planopilaris; lymphocytic hair loss; perifollicular lymphohistiocytic infiltrate; lichenoid pattern; immune privilege (ip) collapse.

1.Introduction:

Frontal fibrosing alopecia (FFA) and Lichen planopilaris (LPP) are inflammatory scarring hair loss disorders primarily affecting premenopausal and postmenopausal women. These forms of primary cicatricial alopecias (PCAs) lead to disfiguring hair loss, significant scalp symptoms, secondary cutaneous morbidity, and severely reduced quality of life (QOL), imposing a substantial psychosocial burden on patients. [1]

FFA is an irreversible primary lymphocytic scarring alopecia first described by Kossard in 1994. [2] Prevalence has increased globally since its initial report. [3] Pathogenesis remains unclear, with proposed factors including hormones (oestrogens, androgens, thyroid hormones); [4] environmental factors (cosmetic products, allergens, chemical exposure, or food); [5,6] UV filters, [7] smoking, [8] neurogenic inflammation, [9] peroxisome proliferator-activated receptor-*y* PPAR-*y* dysfunction, [10] promoting epithelial-to-mesenchymal transition and fibrosis; and genetic predisposition, [11] as evidenced by frequent familial segregation (Figure 1). [12]

Clinically, FFA presents with frontal hairline recession seen in 100% of cases. However, the disease may affect both the occipital and temporal areas,

with scarring occurring in up to 96% of individuals. [13-15] Signs of scarring include loss of follicular ostia, local inflammation with perifollicular erythema and scaling, [16] skin pallor accompanied by itching or burning, occasional smooth and lighter than the chronically-sun-exposed forehead, and the lonely hair sign. Scarred hair loss areas on the scalp are pale and show local atrophy with depression of the frontal veins. [17-19] FFA can also involve the eyebrows in up to 50% - 95% of patients and is the primary form of presentation in up to 39% of cases. [20-22] The eyelashes may be affected in 3% of patients, and while other areas, such as the underarms, pubis, and limbs, have a wide range of prevalence ranging from 0 to 77 %. [2,23]

LPP is a prototypical lymphocytic scarring alopecia occurring at the isthmus level and affecting the hair follicle bulge. [24] First described by Pringle in 1895, [25] LPP is considered a follicular variant of lichen planus. [26] It accounts for 40% of primary scarring alopecia. While predominantly affecting women, men can also be affected. [27] The exact cause remains unknown, though Peroxisome Proliferator-Activated Receptor-Gamma (PPAR-γ) dysfunction has been implicated in its pathogenesis PPAR-γ supposedly deletes hair follicle stem cells causing a similar inflammatory reaction that leads to EMT and fibrosis. [28,29] Clinically, LPP predominantly affects the scalp, particularly the vertex, with variable presentation. LPP typically presents with patchy or diffuse hair loss, accompanied by inflammation and scaling around hair follicles, perifollicular erythema and scaling (keratotic spines). The condition progresses toatrophic cicatricial alopecia with loss of follicular ostia. [4] Extracutaneous lichen planus skin lesions may occur in about 50% of cases.13

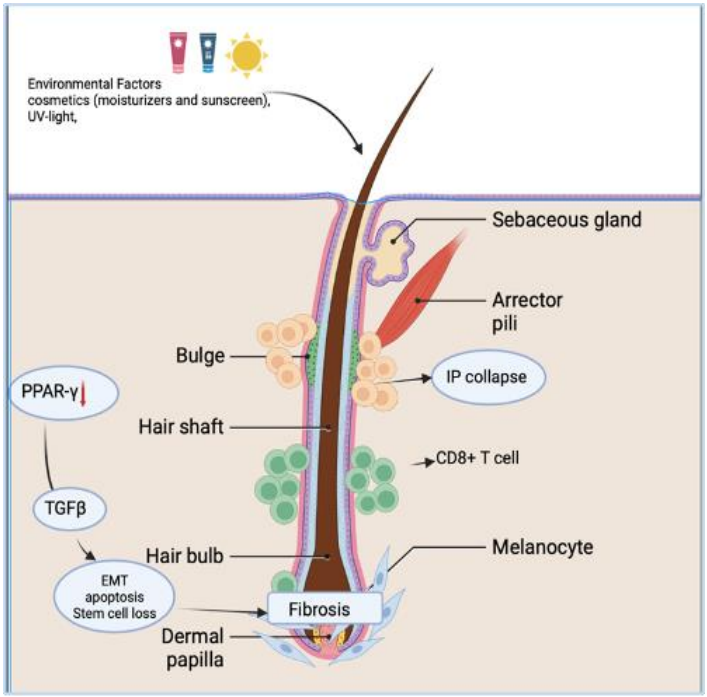

Figure 1: Different hypothetical triggers, such as cosmetics, sunscreen, or stressful conditions, can cause FFA in potentially genetically susceptible individuals. PPAR-γ/TGF-β pathway plays an essential role in EMT and fibrosis. mTOR signalling works as a modulator of PPAR-γ activity and lipid homeostasis.

2.Pathogenesis:

2.1.Immunomodulation:

Mounting evidence suggests that immune system dysfunction and inflammatory processes contribute to the development of FFA and LPP. [30] Several key immune-mediated pathways and inflammatory signals are likely involved.

2.2. Immune privilege collapse and inflammation in FFA and LPP:

Hair follicles (HFs) have a unique microenvironment with a degree of immune privilege (IP) that protects epithelial hair follicle stem cells (eHFSCs) from immune attack. This IP is maintained by mechanisms like the suppression of MHC class I and II pathways and the expression of immunosuppressive molecules like TGF-β2 and CD200.[31-33] However, in FFA and LPP, histological evidence suggests a breakdown of this immune privilege. Studies have shown reduced expression of key IP-maintaining factors like TGF-β2 and CD200 in affected HFs, while markers of immune activation (MHC class I and II) are increased. This disruption creates a pro-inflammatory state, with infiltration of immune cells like CD8+ cytotoxic T cells and plasmacytoid dendritic cells. The exact trigger for this immune privilege collapse remains unclear, and further research is needed to elucidate the sequence of events and identify the underlying cause of the inflammatory processes observed in FFA and LPP. [30,34,35]

2.3. Epithelial-to- mesenchymal transition (EMT) and Fibrosis:

Epithelial-to-mesenchymal transition (EMT) is a natural process involved in embryonic development, wound healing, and tissue repair. However, it can also contribute to pathological conditions like cancer and fibrosis.[36,37] Scarring and fibrosis are hallmarks of FFA and LPP. [38,39] Simple depletion of epithelial stem cells through apoptosis wouldn't explain this fibrosis, as it would lead to tissue loss, not scarring. Studies suggest EMT might play a role in the development of FFA and LPP fibrosis. Elevated levels of EMT markers such as Snail1, Vimentin, and Fibronectin have been observed in affected hair follicles. [40-42] Researchers have also induced EMT in human hair follicles in the lab using specific growth factors, suggesting EMT may contribute to the conversion of epithelial stem cells into scar-forming fibroblasts in FFA and LPP. [28,43,44]

2.4. Peroxisome Proliferator-Activated Receptor γ (PPARγ) and its Potential Role:

PPARγ is involved in fat metabolism and the health of hair follicle oil glands (sebocytes). [45] Reduced PPARγ activity has been linked to fibrosis. [46] Emerging evidence suggests PPARγ may play a significant role in FFA and LPP development. Changes in fat metabolism and reduced activity in hair follicle structures called peroxisomes have been observed in LPP. [29] These changes might contribute to inflammation by allowing the buildup of pro-inflammatory fats within the follicle. Treatment with pioglitazone, a drug that activates PPARγ, has shown promise in managing LPP. Reduced PPARγ activity has been noted in both affected and

unaffected areas of the LPP scalp, suggesting a broader role for this pathway. [26,45,47-49]

The mTOR signalling pathway, which influences hair follicle growth and immune function, is also linked to PPARγ activity. Reduced expression of mTOR pathway proteins has been observed in scalp samples from FFA/LPP patients. More research is needed to identify how the mTOR and PPARγ pathways contribute to FFA and LPP pathogenesis. [50,51] A recent investigation demonstrated that the PPAR-/mTOR signalling pathway in microglia suppresses the expression of tumour necrosis factor (TNF) and interleukin (IL). [52] Additionally, immunohistochemical evaluation of scalp samples from FFA/LPP patients revealed that the expression of all mTOR signalling pathway proteins was reduced in the lesional epidermis of patients. [50] More research is needed to identify how the mTOR and PPAR- pathways, either alone or in combination, contribute to FFA and LPP pathogenesis.

PPARγ activation has been shown to suppress a process called epithelial-to-mesenchymal transition (EMT), which is thought to contribute to scarring in FFA. [28,48] PPARγ agonists may help prevent or reverse EMT, potentially reducing fibrosis. [53-56] Studies have shown that PPAR-γ activation in TGF-β transgenic mice suppresses the TGF-STAT3 and TGF-EGR1 transcriptional activation pathways in various fibrotic disorders, lending credence to the PPAR-γ/TGF- pathway's significance in FFA. [57]

2.5. Genetic and family background:

While the exact genetic cause of FFA and LPP remains unclear, [19,58] there's growing evidence suggesting a genetic predisposition in some cases. [59,60] FFA has been reported in siblings and families, with estimates suggesting a positive family history in 5-8% of cases. Studies have also identified potential links between FFA and specific human leukocyte antigen (HLA) variations.[61-63] This suggests a possible autosomal dominant inheritance pattern with incomplete penetrance, meaning the genetic mutation isn't always expressed in carriers. [64] LPP appears to have a stronger familial link compared to FFA, with documented cases in children and a more even gender distribution. [65,66] Epigenetic factors, which influence gene expression without altering the DNA code itself, might also play a role. [67] Understanding the interplay of genetics and epigenetics in FFA and LPP may provide insights into other hair follicle stem cell disorders. [68]

2.6. Hormonal and neurogenic factors:

While androgens and other hormones are crucial for hair growth, their exact role in FFA and LPP remains uncertain. [69-71] The higher prevalence in postmenopausal women and occasional overlap with androgenetic alopecia (AGA) suggest a possible link to androgens, but evidence is inconclusive. [72,73] The use of 5-alpha reductase inhibitors (5ARIs) has shown mixed benefits. [74-77] Further research is Recent studies suggest a potential role for neurogenic inflammation in FFA. Some patients exhibited increased scalp sweating, and anti-sweat treatments offered temporary relief. However, more research is required to determine if sweating is a cause or consequence of the inflammatory process. [78] However, more research is required to determine if sweating is a cause or consequence of the inflammatory process.

2.7. Environmental Triggers Suspected:

Several factors suggest a possible environmental link to FFA and LPP. [79] The first documented cases of LPP involved follicular spinous eruptions on the scalp associated with generalized lichen planus. Isolated cases link scalp conditions similar to LPP to exposure to chemicals and medications. An increase in reported FFA cases and the location of hair loss on areas exposed to personal care products (PCPs) have led researchers to investigate a connection between FFA and PCPs. [80-82,83] Studies suggest FFA patients may use certain personal care products (PCPs) have led researchers to investigate a connection between FFA and PCPs. [84] Studies suggest FFA patients may use certain PCPs more frequently and might be more sensitive to fragrance ingredients, potentially leading to an immune response. [85,86] Smoking may also be a risk factor for FFA. [87,88] However, more research is needed to confirm these links. Interestingly, the increase in published research on FFA mirrors the rise in reported cases, while LPP research has remained steadier, suggesting a potential role for environmental factors in FFA specifically.

3.Clinical Features:

FFA and LPP, both causing scarring alopecia, can be distinguished by their clinical features. FFA primarily affects postmenopausal women but can also occur in younger individuals and men. [2,3] Similarly, LPP affects both men and women, with a higher prevalence in women. [27] The location of hair loss is a key differentiating factor. FFA typically presents with a receding frontal hairline, potentially extending to the occipital and temporal scalp regions. [13-15] In contrast, LPP manifests as patchy or diffuse hair loss centred on the scalp vertex. [4] Early stages of both conditions may show redness and scaling around remaining hairs. FFA is known for "perifollicular erythema and scaling", [16] while LPP features similar inflammation with "keratotic spines". [4] As the diseases progress, the scalp can become smooth and pale with loss of hair follicles in FFA, and scarring becomes more prominent. [8-10] Eyebrow involvement is common in FFA, affecting up to 95% of patients and sometimes serving as the initial presentation. [21,22] LPP, in its advanced stages, can lead to permanent loss of hair follicles and a smooth, atrophic scalp due to scarring. [13] (Figure 2).

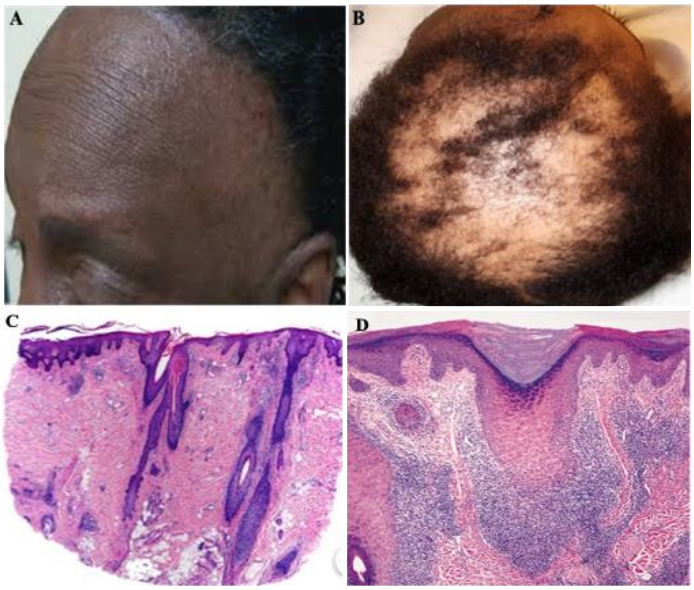

Figure 2: Scarring alopecia: (A) presents FFA with a distinctive clinical pattern of progressive frontotemporal band-like hairline recession and eyebrow loss, (B) presents LPP occurring at the mid-frontal and vertex area of the scalp, (C) FFA histopathology shows perifollicular fibrosis with a moderately dense perifollicular lymphoid cell infiltrate involving several hair follicles. [89] (D) LPP histopathology shows Follicular plugging, hypergranulosis, and dense, band-like perifollicular lymphocytic infiltrate that obscures the infundibular epithelium. [90]

4.Histopathology of FFA and LPP:

FFA exhibits distinct histopathological features depending on the disease progression. The early stages show an inflammatory infiltrate containing lymphocytes and histiocytes surrounding the outer root sheath, accompanied by mild perifollicular fibrosis. As the disease progresses, pilosebaceous units are replaced by scar tissue, leading to decreased hair density and significant perifollicular fibrosis. [19] A key diagnostic feature in the early stages is the presence of a "follicular triad" consisting of vellus, intermediate, and terminal hairs in various growth phases. [18] This triad results from the inflammatory infiltrate preferentially targeting vellus and intermediate hairs, which are more abundant in the frontal hairline and might express specific antigens that attract the inflammatory cells. [17]

Distinguishing FFA from LPP solely based on histological features remains a challenge. While some studies report potential distinguishing factors like eosinophilic necrosis of the outer root sheath and spared interfollicular epidermis in FFA, [21,91] others haven't found consistent differences. [6,21] Similarly, direct immunofluorescence, a technique helpful in diagnosing LPP, hasn't proven reliable for FFA diagnosis due to variable patterns. [22,23] Consequently, current histological evaluation suggests FFA and LPP might be variants within a larger spectrum of lichenoid alopecia. [91] However, despite these similarities, there are notable differences in demographics, clinical presentation, and potentially underlying pathology between FFA and LPP (Table 1)

Feature	FFA	LPP	Ref
Epidemiology	Common in Postmenopausal women (>60 years). 85% of cases reported are Caucasians.	Adults Women > men	92,93
Clinical manifestation	Involves vellus, intermediate, and terminal hairs	Involves terminal hairs	5,94-103,8-4,8-10,13,15-17
	Yellowish facial papules and pigmented skin patches	Patchy or diffuse alopecia	
	Primarily affects eyebrows	Affects middle-aged population	
	Special manifestations: lonely hair sign, eyelash loss, red or gray dots in eyebrows, depression of frontal veins, pigmented facial macules, limb hair loss, side beard hair loss in males, hypopigmentation under wood lamp	Rarely involves eyebrows	
	Rarely associated with other cutaneous LP variants	Involves skin, mucosal, and nails	
	Associated with androgen deficiency	Associated with androgen excess	
	Band-like distribution around the frontal hairline	Located at frontal hairline or central scalp	
		Peri-follicle erythema; non-scalp areas may be affected	
		Activity at the edge of alopecia	
		Itchy	
Pathology	More necrotic keratinocytes and less inflammatory in comparison infiltrate with LPP, FFA may have inflammation extending below the isthmus in comparison with LPP. - Hypertrophic sebaceous glands with no associated vellus hair follicles. - More frequent terminal catagen-telogen hairs. -Increased Langerhans cells in the infundibuloisthmic region compared to LPP.	More severe inflammatory and less apoptosis, Concentric lamellar fibroplasia - Presence of perivascular infiltrates in the dermis and colloid bodies. - More basilar layer and interfollicular epidermal damage. Increased melanocyte counts in the upper hair follicle. - Increased CD68+ macrophage	6,7,91,96,104

		polarization and upregulated CD163 and IL-4.	
Diagnostic Challenges	Histopathological similarities, such as increased perifollicular lymphocytic infiltration and thick fibrotic tracts, make distinguishing between the two disorders difficult	Initial phases can manifest with subtle symptoms, leading to misdiagnosis or delayed diagnosis	
	Variability in pathologist's expertise and biopsy sample location can result in inconsistent interpretation of biopsy findings		
Treatments	**Topical Therapies**		
	High-potency corticosteroids	Intralesional and topical corticosteroids	105-112
	Intralesional corticosteroids (e.g., triamcinolone acetonide) with lower concentrations to minimize skin atrophy risks	Triamcinolone acetonide (10 mg/mL) every 4 to 6 weeks for localized lesions	
	Calcineurin inhibitors	High-potency topical corticosteroids like clobetasol propionate	
	Systemic Treatments:		
	5-alpha-reductase inhibitors (Finasteride, Dutasteride)	Oral corticosteroids (Prednisone 1 mg/kg/day) for extensive, symptomatic, or rapidly progressing cases	
	Hydroxychloroquine	Significant risks of recurrence and adverse effects	
	Retinoids	Hydroxychloroquine	
	Tetracyclines	Methotrexate	
	Methotrexate		
	Pioglitazone	**Immunomodulators:**	
	Naltrexone	Cyclosporine	
	JAK inhibitors (Tofacitinib)	Naltrexone	
		JAK inhibitors (Tofacitinib)	
	Additional and Emerging Treatments:		
	Naltrexone and other immunosuppressive agents for refractory cases	Refractory LPP Treatments:	
	Diode laser therapy	Systemic retinoids	
	Hair transplant surgery to improve quality of life	Tetracyclines	
		Thalidomide	
		Dapsone	
		Pioglitazone	
		Topical calcineurin inhibitors	
		Griseofulvin	
		Janus kinase inhibitors	
		Oral minoxidil	
	Treatment Challenges:		
	A retrospective study highlighted that 42.9% of patients required multiple drug classes and 11.3% did not achieve a complete response, underscoring the need for effective therapeutic strategies		

Table 1: Clinical and pathological differences between FFA and LPP.

5.Bridging Gaps in Treatment Guidelines: Pathobiology Insights for LPP and FFA:

Despite considerable research efforts, the evidence-based foundation necessary for developing treatment guidelines and predicting outcomes remains insufficient. Critical areas needing further investigation include the exact prevalence and demographic distribution of these disorders, reliable biomarkers for disease activity and therapeutic response, and the roles of genetic, environmental, microbial, cosmetic, and nutritional factors. [113-115]

To overcome these limitations, it is essential to refocus research efforts on the underlying shared and distinct pathobiological mechanisms of LPP and FFA. This approach holds the greatest potential for developing targeted and effective therapeutic interventions. Additionally, it will enable the creation of management strategies tailored to each patient's specific

pathobiology constellation and biomarker expression profile. This review synthesizes recent progress in LPP and FFA pathobiology and proposes concrete avenues for developing more effective treatments.

6.Proteomics Sheds Light on Disease Mechanisms:

Proteomic analysis has provided valuable insights into FFA and LPP, revealing distinct protein patterns in each condition but also some overlap.

In FFA, increased levels of inflammatory markers like interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) suggest a strong inflammatory response. Additionally, proteins involved in extracellular matrix remodelling, such as matrix metalloproteinases (MMPs), are elevated, indicating tissue breakdown and rebuilding. Immune response proteins like HLA-DR and CD68 highlight the involvement of both the body's adaptive and innate immune systems in FFA. [96]

LPP studies identified increased levels of stress-related proteins like heat shock proteins (HSPs) in keratinocytes, suggesting cellular stress as a key factor. The presence of elevated autoantigens and autoantibodies points towards an autoimmune component, with immune system proteins like IgG and complement factors playing a role. Proteins involved in fibrosis, like TGF-β and collagen, are also increased, indicating involvement of scarring processes in LPP hair follicle destruction. [116]

While both FFA and LPP share inflammatory and fibrotic features, they also have unique protein profiles. These distinctions are crucial for developing targeted treatments.

6.1. Proteomics: A Stepping Stone to Personalized Medicine:
By identifying proteins involved in inflammation, immune response, cellular stress, and fibrosis, proteomics has offered potential therapeutic targets. This knowledge is essential for developing more effective and personalized treatments for FFA and LPP. Addressing these areas can pave the way for improved patient quality of life through personalized treatment strategies.

7.Future Directions in FFA and LPP Research:

Despite significant progress in understanding FFA and LPP, critical knowledge gaps remain. Future research efforts should focus on several key areas to improve patient outcomes:

1. **Unveiling the Triggers:**
- **Environmental Factors:** Identifying specific environmental triggers, such as chemical exposures or microbial imbalances, could lead to preventive strategies and targeted therapies.
- **Hormonal Influences:** Elucidating the role of hormones, particularly androgens and their metabolites, in the development and progression of both conditions is crucial. This knowledge could inform the use of hormonal therapies or modulators.
2. **Unravelling the Genetics:**
- **Genetic Predisposition:** Conducting large-scale genetic studies can help identify susceptibility genes and understand their interaction with environmental factors. This could lead to the development of genetic screening tools and potentially personalized medicine approaches.
3. **Targeting the Underlying Mechanisms:**
- **Leveraging Proteomic Insights:** The distinct protein profiles revealed by proteomics offer a wealth of potential therapeutic targets. Developing drugs that target these specific proteins could lead to more effective and personalized treatments for FFA and LPP.
4. **Investigating Neurogenic Inflammation in FFA:**
- **Understanding the Connection:** Further research is needed to determine whether increased sweating in FFA is a cause or consequence of the inflammatory process. This knowledge could inform the development of new treatment strategies, such as topical anti-inflammatory or anti-sweating agents.

8.Conclusion: Unveiling the Complexity and Paving the Way for Personalized Medicine:

Frontal fibrosing alopecia and lichen planopilaris are challenging hair loss disorders. Recent research highlights the roles of immune dysfunction, neurogenic inflammation, potential hormonal influences, and genetic predisposition in FFA and LPP development. Epithelial hair follicle stem cell destruction and epithelial-to-mesenchymal transition are central events driven by chronic inflammation and immune privilege breakdown within the hair follicle.

Proteomic analysis has revealed distinct protein profiles for each condition, offering insights into their molecular landscapes and potential therapeutic targets. Understanding these complex mechanisms is crucial for developing targeted and effective treatment strategies. Future research should focus on:

- Understanding specific triggers (environmental/hormonal)
- Delineating the role of genetics
- Developing targeted therapies based on distinct protein profiles
- Investigating the role of neurogenic inflammation in FFA

By addressing these areas, researchers can move closer to personalized treatment approaches that improve outcomes and quality of life for patients with FFA and LPP.

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