

COMMENTARY **OPEN ACCESS**

# JAK Family Expression and Therapeutic Implications in Primary Cicatricial Alopecias

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## 1 | Context

Primary cicatricial alopecias (PCA) are disorders of unknown etiology marked by irreversible follicular destruction and scarring. The predominant inflammatory infiltrate classifies them: lymphocytic forms such as lichen planopilaris (LPP), frontal fibrosing alopecia (FFA), and central centrifugal cicatricial alopecia (CCCA); neutrophilic forms such as folliculitis decalvans (FD) and dissecting cellulitis; and mixed or nonspecific forms, including acne keloidalis and pseudopelade of Brocq. Subtypes such as FFA and CCCA are increasingly prevalent. Thus, despite their growing prevalence and clinical impact, these disorders remain undercharacterized at the molecular level and lack effective targeted therapies.

## 2 | Key Contributions of the Study

In their recent article in the *International Journal of Dermatology*, Lasheras-Pérez et al. [1] present the first immunohistochemical assessment of JAK proteins in PCA. They show that JAK3 and TYK2 are expressed in lesional infiltrates of LPP, FFA, and FD but are absent in controls. By contrast, JAK1 was uniformly negative and JAK2 positive in all samples, limiting diagnostic value. Notably, TYK2 staining was strongest in FD, a neutrophilic variant. The authors also report a retrospective cohort of 19 LPP patients treated with oral JAK inhibitors, with clinical improvement and acceptable safety. This combined evidence supports the JAK/TYK/STAT pathway as a therapeutic target in these subtypes of PCA.

## 3 | Integration With Previous Evidence

These findings are consistent with transcriptomic studies demonstrating Th1/IFN- $\gamma$  activation and JAK3 skewing in LPP/FFA [2], and with our recent systematic review and meta-analysis of gene expression datasets highlighting interferon-driven and profibrotic programs across PCA [3]. They also echo the phase 2a randomized trial of brepocitinib, a dual TYK2/JAK1 inhibitor, in FFA, LPP, and CCCA, which showed both clinical benefit and suppression of interferon/JAK signaling [4]. Taken together, molecular, histopathologic, and clinical data implicate the JAK/TYK/STAT pathway as a central driver and therapeutic target in PCA, with JAK1/3 and TYK2 emerging as consistent nodes (Figure 1). Notably, the strong TYK2 expression observed in FD suggests that lymphocytic and neutrophilic PCAs may converge on common JAK-STAT-mediated inflammatory and fibrotic mechanisms, opening the possibility of a shared therapeutic approach.

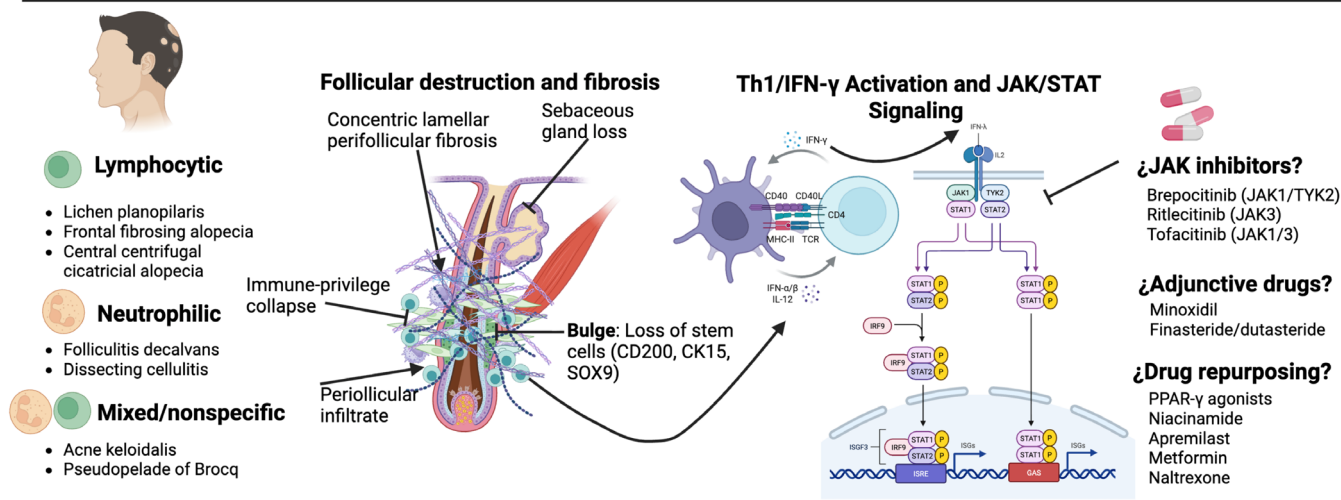
## 4 | Implications and Remaining Challenges

The growing body of evidence underscores the central role of inflammatory and profibrotic pathways, particularly JAK/TYK/STAT signaling, in the pathogenesis of scarring alopecias. These insights provide a strong biological rationale for targeted therapy, yet important knowledge gaps remain. Clarifying how these pathways intersect with disease heterogeneity, stem-cell dynamics, and treatment responses will be crucial to translating molecular findings into durable clinical benefit. This raises the prospect of a common therapeutic strategy, although critical challenges remain:

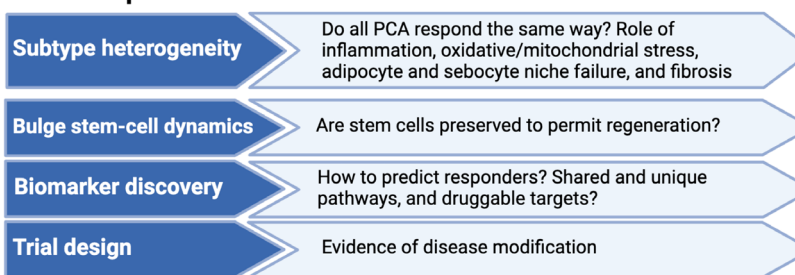
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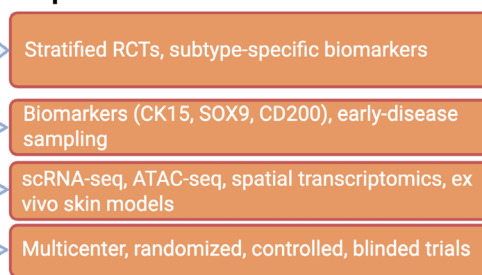
# Primary Cicatricial Alopecias (PCA)



## Research priorities and unmet needs



## Proposed Actions



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**FIGURE 1** | Overview of primary cicatricial alopecias: clinical subtypes, shared pathogenic mechanisms, current therapeutic approaches, and unmet needs in translational and clinical research.

- **Subtype heterogeneity and biomarker development.** Responses are likely to differ across subtypes, reflecting distinct pathogenic mechanisms identified in recent transcriptomic studies and systematic reviews—including oxidative and mitochondrial stress, or adipocyte and sebocyte niche failure—which shape the balance between active inflammation and established fibrosis [3]. A deeper understanding of disease biology is therefore required to stratify responders and define treatment windows. Beyond integrating immunohistochemistry, transcriptomics, and clinical indices, single-cell RNA-seq/ATAC-seq, spatial transcriptomics, and ex vivo organ-skin culture models could help unravel the shared and unique features of PCA subtypes and their dynamic progression, providing the basis for rational biomarker discovery and targeted intervention.
- **Bulge stem-cell preservation and timing.** We still do not know if the bulge stem cell pool endures long enough to permit regeneration once inflammation is controlled. Early disease may retain this capacity [2], but in advanced stages, fibrosis likely reflects permanent depletion of progenitors. Incorporating bulge stem-cell biomarkers (e.g., CK15, SOX9, CD200) into early clinical development will be essential to define therapeutic windows and determine whether JAK inhibition can truly alter the trajectory of scarring alopecias.
- **Adjunctive therapies.** Another unresolved question is whether JAK inhibitors should be used as monotherapy or in combination with established adjuvants. Finasteride,

dutasteride, and minoxidil have been proposed as supportive agents in FFA and LPP, acting through hormonal or follicular survival pathways. Their combination with JAK inhibition may enhance efficacy or prolong remission, but it remains to be clarified whether current off-label use of these agents is truly well directed or requires refinement through randomized controlled studies, underscoring the need for careful evaluation in the clinical setting.

- **Therapeutic direction.** Future research should prioritize mechanism-based small molecules with robust translational rationale, particularly those targeting the JAK/TYK/STAT axis, TGF- $\beta$  signaling, and profibrotic pathways [3]. In parallel, drug repurposing strategies such as PPAR- $\gamma$  agonists, metformin, niacinamide, apremilast, or low-dose naltrexone merit systematic evaluation. These agents have been postulated on the basis of their potential to modulate inflammation, metabolic stress, or fibrotic remodeling, yet current evidence remains limited and largely anecdotal, underscoring the need for rigorous pre-clinical and clinical validation. By contrast, interventions with limited or inconsistent evidence—such as platelet-rich plasma or nutritional supplements—remain speculative [5]. While occasionally used in practice, they should not divert resources or patient expectations away from the development of rational, disease-modifying strategies supported by molecular and clinical data.

## 5 | Concluding Remarks

Lasheras-Pérez et al. provide compelling protein-level evidence of JAK3 and TYK2 activation in PCA, complementing transcriptomic findings and preliminary clinical trial data. While not sufficient to justify routine clinical use, their work points in the right direction, opening the door for rigorous, multicenter, controlled, and blinded randomized trials. Such studies will be essential to determine whether JAK inhibition can move beyond biological plausibility to therapeutic reality—capable not only of suppressing inflammation but also of reshaping the fibrotic course of scarring alopecias.

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### Conflicts of Interest

The author declares no conflicts of interest.

### Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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