similar between groups. Patients with HS developed their first SCC at a younger age than did controls (58.9 years vs. 62.2 years, \( P = 0.026 \)) but developed their first BCC at a similar age to controls (58.8 years vs. 55.9 years, \( P = 0.052 \)). Risk of BCC and SCC stratified by sex did not differ between cases and controls.

Similar to our findings, studies suggest that SCCs arising at HS sites predominantly occur in men and in the buttocks or perineum.\(^3,5\) For KCs located at any site, a study on hospitalized Swedish patients found increased SCC risk associated with HS; BCC risk was not examined.\(^2\) However, the study did not account for SCC risk factors or surveillance bias, and it only reported a SCC incidence rate of 24 out of 100 000 person-years among 2119 patients with HS in contrast to our study’s reported a SCC incidence rate of 24 out of 100 000 person-years among 4604 patients with HS, which is more consistent with published SCC disease estimates,\(^7\) suggesting potential incomplete ascertainment of SCCs.\(^3\)

Strengths of our study include adjusting for some known KC risk factors and dermatologist surveillance, examining a large and racially diverse patient sample, and quantifying both BCC and SCC risk. Study limitations include inability to account for certain risk factors (e.g. sun exposure) and use of a single institutional data source. Our results suggest that patients with HS have reduced risk of BCC, but similar risk of SCC, compared with those with acne. However, patients with HS develop SCCs at a younger age than those with acne. Our findings may reflect different mechanistic pathways involved in disease pathogenesis, differential exposure to sunlight and other environmental factors that affect skin cancer risk, or distinct treatment paradigms as patients with HS are often exposed to immunosuppressive regimens.\(^8\) Chronic inflammation may also contribute to the younger age of SCC development among patients with HS.\(^4\) Further studies are needed to replicate our findings in other populations. Our findings have implications for clinicians caring for patients with HS, who may benefit from increased awareness of their risk of SCC arising at a younger age, when performing skin examinations.

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Does mitochondrial dysfunction of hair follicle epithelial stem cells play a role in the pathobiology of lichen planopilaris?

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Dear Editor, Lichen planopilaris (LPP) is a difficult-to-treat condition leading to permanent hair loss and scarring.\(^1\) Pathobiologically, LPP shows T-cell-mediated interferon-\(\gamma\)-driven loss of keratin 15-positive hair follicle (HF) epithelial stem cells (eHFSCs) due to immune privilege (IP) collapse and pathological epithelial-to-mesenchymal transition (EMT).\(^1,2\) This exhausts the eHFSC pool, impacting the HF’s capacity to regenerate and cycle, ultimately resulting in HF destruction, fibrosis and scarring.\(^1\)

Defective or insufficient peroxisome proliferator-activated receptor (PPAR)-\(\gamma\) signalling in eHFSCs has been implicated in LPP pathogenesis,\(^3\) which can be partly rescued by PPAR-\(\gamma\) agonists.\(^2\) However, currently available systemic PPAR-\(\gamma\) agonists also stimulate PPAR-\(\alpha\) and therefore have potential for considerable adverse effects, highlighting a need to identify more effective treatment strategies that target central elements of LPP pathobiology.

In the current pilot study we explored the possibility that mitochondrial dysfunction in eHFSCs may represent one such
target in LPP pathobiology. Apart from the increasing appreciation of keratinocyte mitochondrial function in HF biology, this hypothesis was encouraged by our recent finding that PPAR-γ stimulation profoundly upregulates mitochondrial activity in organ-cultured human scalp HFs. Therefore, we investigated whether eHFSCs in lesional human LPP HFs show indications of mitochondrial dysfunction.

To investigate mitochondrial function in LPP we first searched for ultrastructural mitochondrial abnormalities in outer-root-sheath keratinocytes below the level of the sebaceous gland, including the bulge region, by transmission electron microscopy. Compared with healthy HFs, which had small cylindrical mitochondria, both nonlesional and lesional LPP HFs (five patients) showed mitochondria that had undergone swelling, being rounded and enlarged or swollen (Figure 1a). Notably, in nonlesional HFs, most mitochondria retained their inner-membrane cristae, suggesting they are still at least partially functional. However, the cristae were found to be completely degenerated in lesional HFs, which is a characteristic ultrastructural sign of severe mitochondrial damage and/or mitochondrial leakage.

Mitochondrial transcription factor A (TFAM) is critical for mitochondrial DNA transcription and genome replication and is upregulated by PPAR-γ in human HFs. Therefore, we next investigated TFAM protein expression by quantitative and standardized immunohistomorphometry of keratin 15-positive cells in lesional and nonlesional LPP, and healthy HFs. TFAM immunoreactivity was significantly lower in lesional HFs than in healthy or nonlesional HFs in the bulge (P = 0.003), with nonlesional HFs showing a slight but nonsignificant decrease compared with controls (Figure 1b). As TFAM is essential for mitochondrial genome replication, transcription and packaging, defective or insufficient TFAM, even in nonlesional HFs, suggests that these HFs have a constitutive problem in TFAM expression, which might contribute to the ultrastructural...
mitochondrial abnormalities observed (Figure 1a). Preliminary evidence suggests that HFs may attempt to compensate by upregulating MT-CO1 and VDAC1, but this requires further investigation (unpublished work by R.P.).

Next, to probe how the controlled induction of EMT and IP collapse affected bulge mitochondrial function, we utilized a ‘cocktail’ to promote EMT and IP collapse in the bulge of healthy human scalp HFs, thereby imitating LPP pathogenesis ex vivo.1,2 Vimentin and E-cadherin expression was used to verify EMT induction in treated HFs (not shown).

A significant decrease in the expression of TFAM in the bulge of healthy anagen scalp HFs was observed following 3 days of cocktail treatment (Figure 1c). Moreover, the respiratory rate of cocktail-treated HFs was drastically reduced compared with vehicle-treated control HFs, as assessed by O2 consumption assay (Figure 1d). These data suggest that a proinflammatory signalling milieu sufficient to induce bulge IP collapse and EMT also promotes mitochondrial dysfunction in human eHSCs.

Together, our gene and protein expression, ultrastructural and energy metabolism data highlight a functionally important role of eHSC mitochondrial dysfunction in LPP development. This not only introduces an important new principle into LPP pathobiology, but further encourages systematic exploration of novel mitochondrial stimulatory agents that target eHSCs in LPP management.2

Going forward, future research following up this pilot study firstly needs to elucidate whether mitochondrial defects are secondary to LPP-associated HF inflammation or represent a constitutive abnormality that predisposes to eHSC damage and LPP development; this could in part be investigated by ultrastructural analysis of mitochondria after EMT induction. Secondly it should be examined how bulge mitochondrial dysfunction is acquired, how it progresses and whether it is reversible therapeutically. On this basis, it would be interesting to investigate PPAR-γ coactivator α, whose expression is increased upon mitochondrial dysfunction.3 Thirdly, it would be useful to investigate whether and how mitochondrial dysfunction contributes to bulge IP collapse and/or pathological EMT. Finally, we need to understand whether this dysfunction is linked to LPP-associated abnormalities in PPAR-γ-mediated signalling and whether PPAR-γ-specific agonists may be therapeutic in stimulating HF epithelial mitochondrial function, given the recognized impact of the latter on mitochondrial HF physiology.5,8

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Outcome domains in lichen sclerosus

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Dear Editor, Lichen sclerosus (LS) is a chronic inflammatory dermatosis predominantly affecting the genitals. It can affect men, women and children. LS affecting female genitalia typically presents with itchy patches that impact on physical and psychosocial-sexual functioning.1,2 Symptoms in men include difficulty urinating due to urethral narrowing, difficulty in foreskin retraction due to scarring, and dyspareunia. Complications include loss of anatomy and malignant transformation.

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