The Specific Immune Mechanism of **Lichen Planus** May Lead to a **Specific Treatment**

The inflammation in cutaneous lichen planus is dominated by IFN-ϒ and IL-21—A basis for therapeutic JAK1 inhibition

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Cutaneous lichen planus (CLP) and psoriasis (PSO) are both common chronic inflammatory skin diseases for which development of new treatments requires the identification of key targets. While PSO is a typical Th17/IL-17-disorder, there is some evidence that Th1/IFN-ϒ dominate the inflammatory process in CLP. Nonetheless, the immunopathogenesis of CLP is not fully explained and key immunological factors still have to be recognized. In this study, we compared the immune signature of CLP lesions with the well-characterized inflammation present in PSO skin. First, we analysed the histological and immunohistological characteristics of CLP and PSO. Second, we assessed the cytokine expression (IL1A, IL1B, IL4, IL6, IL8, IL10, IL17A, IL19, IL21, IL22, IL23A, IL13, IFNG, TNF, IL12A, IL12B and IL36G) of lesional skin of CLP with PSO by qPCR. Histology revealed a similar epidermal thickness in CLP and PSO. Immunohistochemically, both diseases presented with an inflammatory infiltrate mainly composed by CD3+CD4+ T cells rather than CD3+CD8+. Importantly, mRNA analysis showed a distinct cytokine signature: while levels of IL12B, IL1A, IL6 and IL23 were similar between the two groups, the characteristic PSO-associated cytokines IL8, IL17A, IL22, IL19 and IL36G were expressed at very low levels in CLP. In contrast, CLP lesional skin was dominated by the expression of IFNG, IL21, IL4, IL12A and TNF. Immunohistochemistry confirmed the dominance of IL-21, IFN-ϒ and also pSTAT1 in the dermal infiltrate of CLP, while IL-17A was more present in PSO. Collectively, this study improves our understanding of the immunological factors dominating CLP. The dominating cytokines and signalling proteins identified suggest that anti-cytokine therapeutics like JAK inhibitors may be beneficial in CLP.

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The Best Therapy Against **PalmoPlantar Pustulosis** is: **STOP SMOKING**

Cigarette smoke underlies the pathogenesis of palmoplantar pustulosis via an IL-17A-induced production of IL-36γ in tonsillar epithelial cells

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Palmoplantar pustulosis (PPP) is characterized by sterile pustules on the palms and/or soles. A strong association between PPP and tobacco smoking has been reported, and it has been speculated that the interleukin (IL)-17A pathway may play an important role in PPP. Recent studies have suggested that IL-36 plays a pivotal role in the pathogenesis of psoriasis and its subtypes. The relationships among IL-36, smoking, and PPP have not been examined. Here, we investigated the relationships among the smoking index, severity of the clinical condition of PPP, and in vitro dynamics of IL-36 in human tonsillar epithelial cells under the condition of exposure to a cigarette smoke extract (CSE). The results demonstrated that the Palmoplantar Pustulosis Area and Severity Index (PPPASI) was strongly and positively correlated with the smoking index in female patients. Immunohistochemical examinations showed that IL-36γ was highly expressed in tonsillar epithelial cells from PPP patients but not in those from recurrent tonsillitis patients without PPP. The in vitro study revealed that IL-17A synergistically induced a release of IL-36γ under CSE exposure. These results suggest that local production of IL-36γ by epithelial cells induced by cigarette smoke exposure plays an important role in the pathogenesis of PPP.

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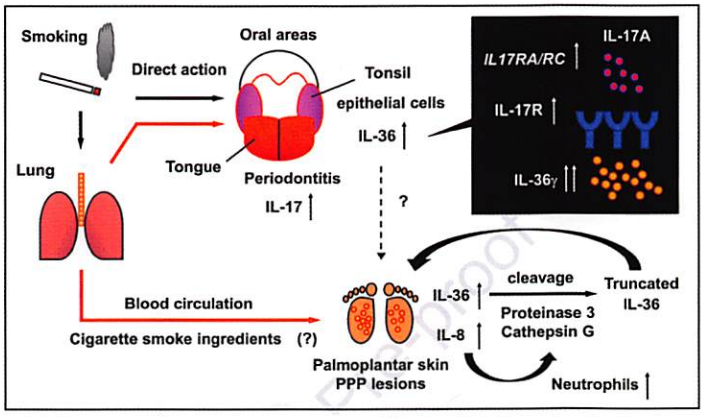
Figure 5



Association of Clinical and Demographic Factors With the Severity of Palmoplantar Pustulosis

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Importance: Although palmoplantar pustulosis (PPP) can significantly impact quality of life, the factors underlying disease severity have not been studied.
Objective: To examine the factors associated with PPP severity.
Design, Setting, and Participants: An observational, cross-sectional study of 2 cohorts was conducted. A UK data set including 203 patients was obtained through the Anakinra in Pustular Psoriasis, Response in a Controlled Trial (2016-2019) and its sister research study Pustular Psoriasis, Elucidating Underlying Mechanisms (2016-2020). A Northern European cohort including 193 patients was independently ascertained by the European Rare and Severe Psoriasis Expert Network (2014-2017). Patients had been recruited in secondary or tertiary dermatology referral centers. All patients were of European descent.

The PPP diagnosis was established by dermatologists, based on clinical examination and/or published consensus criteria. The present study was conducted from October 1, 2014, to March 15, 2020.

Main Outcomes and Measures: Demographic characteristics, comorbidities, smoking status, Palmoplantar Pustulosis Psoriasis Area Severity Index (PPPASI), measuring severity from 0 (no sign of disease) to 72 (very severe disease), or Physician Global Assessment (PGA), measuring severity as 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), and 4 (severe).

Results: Among the 203 UK patients (43 men [21%], 160 women [79%]; median age at onset, 48 [interquartile range (IQR), 38-59] years), the PPPASI was inversely correlated with age of onset (r=−0.18, P=.01). Similarly, in the 159 Northern European patients who were eligible for inclusion in this analysis (25 men [16%], 134 women [84%]; median age at onset, 45 [IQR, 34-53.3] years), the median age at onset was lower in individuals with a moderate to severe PGA score (41 years [IQR, 30.5-52 years]) compared with those with a clear to mild PGA score (46.5 years [IQR, 35-55 years]) (P=.04). In the UK sample, the median PPPASI score was higher in women (9.6 [IQR, 3.0-16.2]) vs men (4.0 [IQR, 1.0-11.7]) (P=.01). Likewise, moderate to severe PPP was more prevalent among Northern European women (57 of 134 [43%]) compared with men (5 of 25 [20%]) (P=.03). In the UK cohort, the median PPPASI score was increased in current smokers (10.7 [IQR, 4.2-17.5]) compared with former smokers (7 [IQR, 2.0-14.4]) and nonsmokers (2.2 [IQR, 1-6]) (P=.003). Comparable differences were observed in the Northern European data set, as the prevalence of moderate to severe PPP was higher in former and current smokers (51 of 130 [39%]) compared with nonsmokers (6 of 24 [25%]) (P=.14).

Conclusions and Relevance: The findings of this study suggest that PPP severity is associated with early-onset disease, female sex, and smoking status. Thus, smoking cessation intervention might be beneficial.

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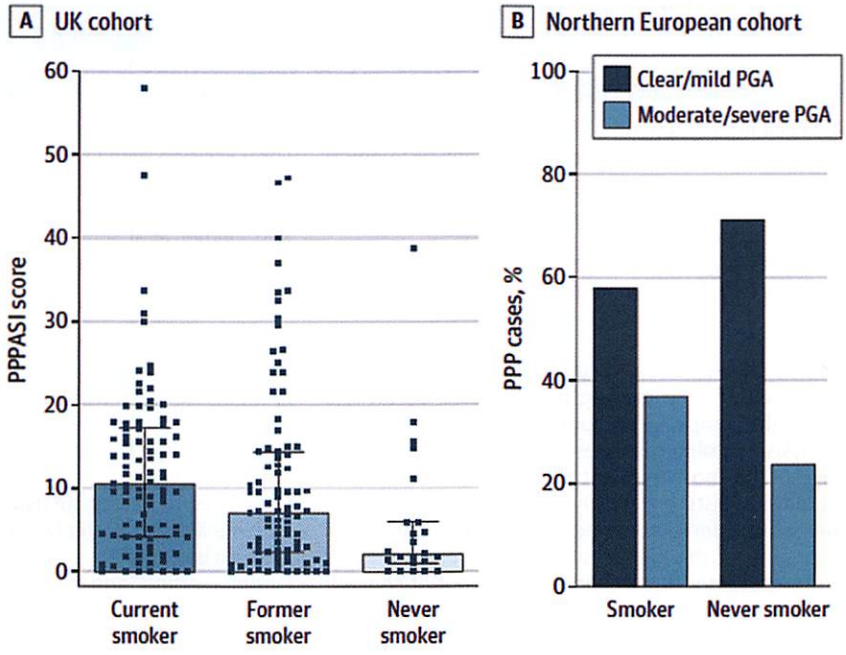
Figure 3. Disease Severity Scores in Current, Former, and Never Smokers



A, In the UK cohort, Palmoplantar Pustulosis Psoriasis Area Severity Index (PPPASI) scores are highest in current smokers, intermediate in former smokers and lowest in never smokers. Data are presented as median (interquartile range). P < .01 per Kruskal-Wallis test. B, In the Northern European sample, the proportion of individuals with moderate to severe disease was elevated in current and former smokers compared with never smokers. Physician Global Assessment (PGA) measures severity as 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), and 4 (severe). PPPASI measures severity with scores from 0 (no sign of disease) to 72 (very severe disease). PPP indicates palmoplantar pustulosis.