FROM THE DERMATOLOGY FOUNDATION

Skin-infiltrating, interleukin-22–producing T cells differentiate pediatric psoriasis from adult psoriasis

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Background: Evidence from adult psoriasis studies implicates an imbalance between regulatory and effector T cells, particularly T_H-17–producing T cells, in the pathogenesis of psoriasis. Little is known about the immunopathology of psoriasis in children.

Objective: We sought to functionally characterize the inflammatory cell profiles of psoriatic plaques from pediatric patients and compare them with healthy, age-matched controls and adult psoriasis patients.

Methods: Skin samples from pediatric psoriasis patients and healthy controls were analyzed by multiparameter flow cytometry to determine the dominant immune cell subsets present and cytokines produced.

Results: Lesional tissue from pediatric psoriasis patients had significantly increased interleukin (IL) 22 derived from $CD4^+$ and $CD8^+$ cells compared with the tissues from healthy pediatric controls and adult psoriasis patients. Tissue from pediatric psoriasis patients had significantly less elevation of IL-17 derived from $CD4^+$ and $CD8^+$ cells compared with the tissue from adult psoriasis patients. In contrast with the lesions from adult patients, lesional skin in pediatric patients with psoriasis did not have increases in regulatory T cells.

Limitations: This is a pilot study, thus the sample size is small.

Conclusion: Significant differences in IL-17 and IL-22 expression were observed in the pediatric psoriasis patients compared with pediatric healthy controls and adult psoriasis patients. IL-22 might be relevant in the pathogenesis of pediatric psoriasis and represents a potential treatment target unique to pediatric psoriasis. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.05.017.)

Key words: IL-17; IL-22; immunophenotype; pediatric psoriasis; psoriasis.

Psoriasis is a T-cell–mediated, chronic inflammatory skin condition that affects children and adults. Evidence from studies with adult psoriasis patients implicates an imbalance between regulatory and effector T cells, particularly T_H-17–producing T cells, in the pathogenesis of psoriasis.[1-3] Pediatric psoriasis often differs from adult psoriasis in presentation, triggers, natural history, and response to therapy, suggesting potential differences in the pathophysiology of the disease processes.[4] To date, studies examining the immunology of psoriasis have largely focused on adult patients. In psoriasis patients, innate and adaptive immune responses are thought to stimulate T-cell activation and

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induce helper T-cell differentiation to produce proinflammatory cytokines, including interferon (IFN) γ, interleukin (IL) 17, IL-22, IL-23, and tumor necrosis factor (TNF) α.[5] Serum cytokine levels have been determined to be significantly higher in adult patients with active psoriasis compared with controls.[6] Multiple groups have looked at serum cytokine levels in association with clinical disease severity and found that increased levels of cytokines IFN-γ, IL-6, IL-12, IL-17, IL-18, IL-20, IL-22, and IL-23 positively correlated with severity of psoriasis.[6,7] Analysis of the cell and cytokine composition in active psoriasis plaques of adult patients has confirmed a change in the composition of skin inflammatory cells, further suggesting that inflammatory cytokines are responsible for driving the disease process. Nograles et al proposed a working model in which normal dermal $CD4^+$ cells that produce IL-17 and IL-22 become pathogenic during inflammation and stimulate the production of chemokines that attract neutrophils to the psoriatic lesions.[8] Using a multiparameter flow cytometric approach, we have found that psoriatic lesional skin had increased numbers of regulatory T cells (T regs) and that these cells produced more IL-17 when compared with T regs found in nonlesional skin.[2] These findings potentially explain why adult psoriasis responds to targeted biologic therapies against TNF-α and IL-17, among others.

Although there are robust clinical and molecular data to guide treatment innovations for adult psoriasis, psoriasis in children remains understudied. To date in the United States, only 1 systemic therapy is licensed for use by the Food and Drug Administration to treat psoriasis in children. The TNF-α inhibitor etanercept was approved in November 2016 for moderate-to-severe plaque psoriasis in children $\geq$4 years of age.[9] This approval was based largely on data from 2 clinical trials.[10,11] Little is known about the immunologic differences between childhood and adult psoriasis that might correlate with the observed clinical differences between the 2 populations. Although the immune composition of the peripheral blood of pediatric psoriasis patients has been recently reported,[3] the cutaneous inflammatory cell infiltrates and cytokine profiles of lesional psoriatic skin from children has not been defined. Identifying the specific inflammatory cell and cytokine milieu in children is the next step towards understanding the potential molecular underpinnings of the observed clinical differences and might identify optimal treatment targets. To this end, using multiparameter flow cytometry, we functionally characterized the cell profiles of psoriatic plaques of pediatric patients and compared them with the inflammatory profiles of healthy, age-matched controls and adult psoriasis patients.

CAPSULE SUMMARY

- Little is known about the pathophysiology of pediatric psoriasis.
- Increased expression of interleukin (IL) 22 relative to IL-17 was observed in pediatric compared with adult psoriasis patients.
- Elevated expression of IL-22, more so than IL-17, in pediatric compared to adult psoriatic plaques suggests an additional potential treatment target unique to pediatric psoriasis.

METHODS

Participants

Psoriatic skin samples were obtained from a consecutive sample of consenting children who presented to the University of California, San Francisco (UCSF), Pediatric Dermatology Clinic for routine clinical care. Study patients were recruited at the time of clinical visits and from a contact list of patients with psoriasis who indicated willingness to participate in clinical studies. All patients provided written, informed consent, and for minors, dual parental consent and patient assent was obtained before enrollment in the study. Detailed clinical characteristics were recorded by study personnel and included patient demographics, family history, age of onset, comorbidities, morphologic subtype, distribution, and psoriasis body surface area (BSA) of involvement. Disease activity was scored by using clinician judgment and disease severity by using a psoriasis severity grading scale as follows: mild <10% BSA, moderate 10%-20% BSA, severe >20% BSA, very severe >50% BSA. Patients 4-20 years of age with active psoriasis were eligible to be included in the study. Exclusion criteria included use of any systemic or phototherapy within 4 weeks or topical treatment within 2 weeks of enrollment.

Normal skin was obtained from pediatric patients undergoing plastic surgical reconstructive or excisional procedures at UCSF from which benign normal tissue margins were available and would have otherwise been discarded. Adult psoriasis skin from patients 20-76 years of age was obtained from the UCSF General Dermatology clinics. Normal, healthy adult skin was obtained from patients undergoing elective surgery at UCSF and has been detailed elsewhere.[2] Site, age, and sex data were available for all normal control tissues in accordance