

LETTER TO THE EDITOR

Keloid lesions show increased IL-4/IL-13 signaling and respond to Th2-targeting dupilumab therapy

Editor

Keloids are benign growths representing a disrupted wound healing process involving abnormal collagen proliferation. Keloids are most prevalent in African American (AA)¹ and Asian populations,² and greatly impact quality of life.³ Keloids show high recurrence rates and current therapies (intralesional steroids, bleomycin, surgical excision, etc.) have limited efficacy,⁴ thus, presenting a high unmet need for better treatments. Genetic studies have identified chromosome variants associated with keloid formation in AAs and Asians.^{1,5} A genomic profiling study on lesional and non-lesional keloid skin from three AA patients identified bone/cartilage abnormalities,⁶ but did not assess inflammatory pathways. Recently, atopic dermatitis (AD) has been indicated as an independent risk factor for developing keloids.⁷ Increases in IL-4 and IL-13 receptors have been detected through laser capture microdissection in lesional keloid skin, but increases in cognate ligands were not detected.⁸

We present a 53-year-old AA male who presented with severe AD (Body Surface Area/BSA 70%; Scoring of AD/SCORAD, 50; Eczema Area and Severity Index/EASI, 33), postinflammatory hypopigmentation and two nodules: a large prominent exophytic nodule with raised borders and a smaller adjacent nodule on the right popliteal fossa, surrounded by a large area of hard indurated skin, which lacked normal skin lines, present for >2 years. Both nodules were diagnosed clinically and histologically (with prominent fibrosis and mononuclear cells) as keloids (Fig. 1a,b), previously managed with multiple (>6) intralesional triamcinolone injections with minimal improvement. Patient was started on 300 mg subcutaneous dupilumab injections for severe AD, given every 2 weeks, in August 2018. Seven months after dupilumab, there was significant AD improvement (BSA 8%; SCORAD, 16; EASI, 10), with overall reduction of the fibrotic plaque by ~50% and shrinkage of the large keloid, flattening of the surrounding borders and complete disappearance of the smaller keloid (Fig. 1c). Of note, normal skin lines are visible only after treatment (Fig. 1b,c).

As a result of successful keloid response to dupilumab, we used real-time PCR to evaluate Th2 gene expression (IL-4R, IL-13 and CCL18) in lesional and non-lesional keloid skin from

three previously reported AA patients (3 females, mean age, 47.3 years) with severe chronic keloids and no concurrent AD.⁶ Five healthy AA controls (2 females, 3 males, mean age, 39.8 years) were included for comparisons. Six-millimeter whole-skin biopsy specimens were obtained from the extremities under IRB-approved protocols.

IL-4R, directly targeted by dupilumab, was highly up-regulated in keloid lesions versus controls ($P < 0.1$; Fig. 1d). A key Th2 cytokine, IL-13, was significantly increased in lesional and non-lesional keloids versus controls, despite the limited sample size ($P < 0.05$; Fig. 1e). Th2 chemokine, CCL18, was highly increased in keloids, particularly in non-lesional skin ($P < 0.05$; Fig. 1f). We next validated genes involved in cartilage/bone development, previously reported as highly expressed in keloids,⁶ including cadherin-11 and fibrillin-2, among others; all significantly increased in keloid lesions versus controls and versus non-lesional skin ($P < 0.05$; Fig. 2).

This is the first report of keloid improvement with dupilumab that blocks type 2-driven inflammation via IL-4/IL-13 signaling and approved for moderate-to-severe AD.⁹ This suggests a potential underlying Th2 pathogenesis driving keloid formation.

To our knowledge, this is the first report identifying Th2-skewing including increased IL-13 production in chronic lesional and also non-lesional keloid skin in patients without a background of AD. This, together with the increased IL-4/IL-13 receptor expression in keloids,⁸ provides potential mechanistic insight into the keloid response to dupilumab. IL-13, increased in both lesional and non-lesional keloid skin, was shown in *ex-vivo* fibroblasts to enhance TGF- β signaling and promote fibrosis via periostin,¹⁰ an effect potentially suppressed by dupilumab. The fact that IL-13, along with the Th2 chemokine CCL18, was also increased in non-lesional skin of keloid patients perhaps suggests that the entire integument of patients with severe keloids is abnormal and prone to additional keloid formation, supporting for use of systemic treatments.

This preliminary report demonstrates a novel use of dupilumab for chronic keloids, showing major reductions in skin fibrosis and keloidal scarring. We show up-regulated levels of Th2 cytokines in both lesional and non-lesional keloid skin, suggesting their potential pathogenic involvement and therapeutic potential. The association of keloids and Th2 axis may also be suggested by the higher risk for keloid formation in AD patients.⁷ Dupilumab and other Th2-targeting agents may provide treatment options for patients with severe keloids, warranting further studies.

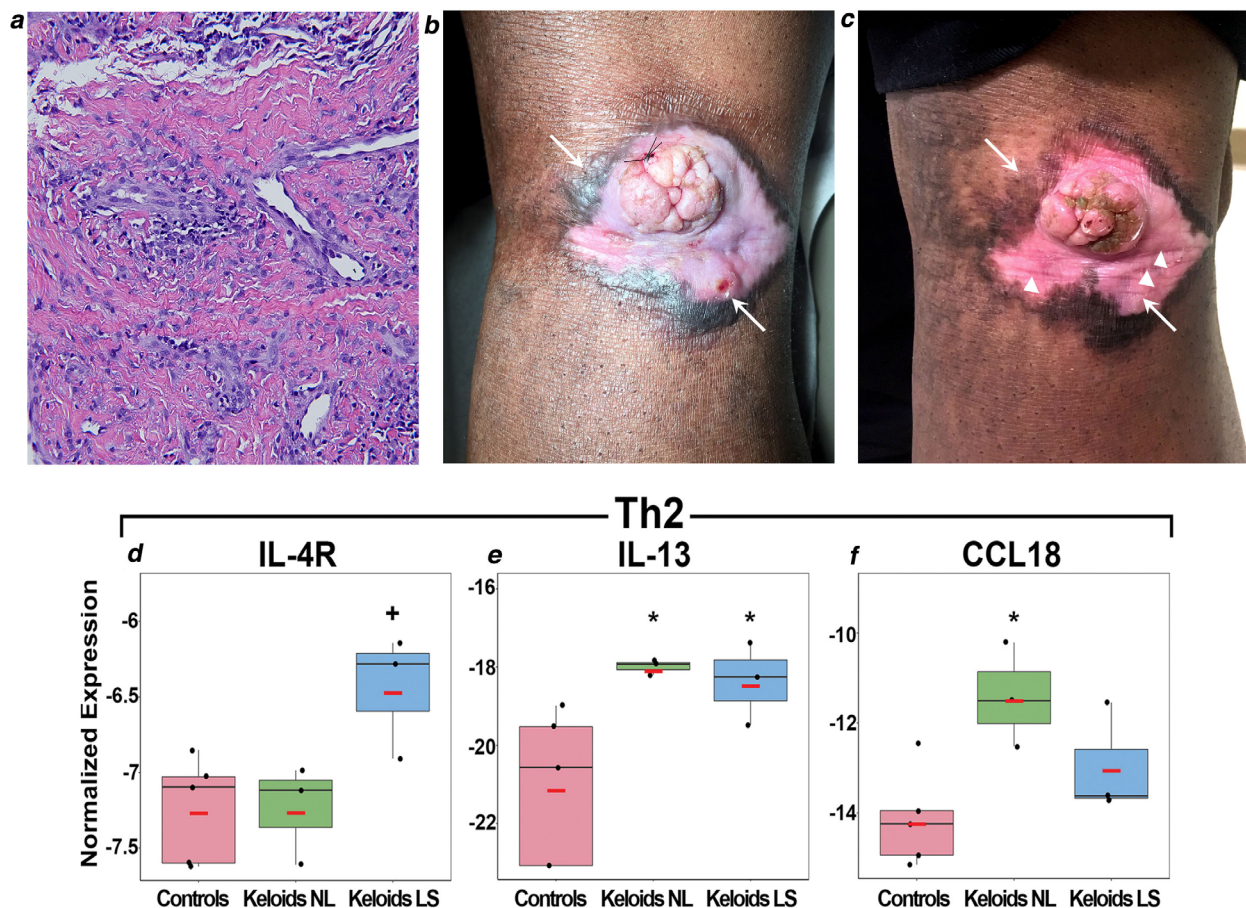


Figure 1 Histological image, clinical findings before and after dupilumab treatment, and expression of inflammatory biomarkers. (a) Histological image showing marked fibrosis and accompanying mononuclear cells. (b) On the right popliteal fossa, on a background of a large fibrotic plaque measuring $\sim 5.5 \times 5$ cm, there is a sizeable exophytic depigmented keloid, and a smaller keloid in the inferior margin, August 2018. Biopsy sites are marked by a suture or an arrow. (c) Following dupilumab treatment, the fibrotic plaque has regressed $\sim 50\%$, with complete disappearance of the smaller keloid (arrow), and vertical shrinkage of the large keloid, March 2019. Arrowheads mark return of normal skin lines. Upon regression of the fibrotic area, margins show marked postinflammatory hyperpigmentation in otherwise normal appearing skin. Photographs published with patient permission. Th2-specific inflammatory biomarkers (d–f) measured by quantitative real-time PCR in healthy skin and keloid non-lesional (NL) and lesional (LS) skin. Black stars: significance of comparison between keloid skin and controls. Black lines within boxes represent median values; bold red lines represent mean values. Each black dot represents an individual patient; $^+P < 0.1$, $*P < 0.05$.

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References

- Hellwege JN, Russell SB, Williams SM, Edwards TL, Velez Edwards DR. Gene-based evaluation of low-frequency variation and genetically-

predicted gene expression impacting risk of keloid formation. *Ann Hum Genet* 2018; **82**: 206–215.

- Lu WS, Zheng XD, Yao XH, Zhang LF. Clinical and epidemiological analysis of keloids in Chinese patients. *Arch Dermatol Res* 2015; **307**: 109–114.
- Bijlard E, Kouwenberg CA, Timman R *et al*. Burden of keloid disease: a cross-sectional health-related quality of life assessment. *Acta Derm Venerol* 2017; **97**: 225–229.
- Huang C, Liu L, You Z, Du Y, Ogawa R. Managing keloid scars: from radiation therapy to actual and potential drug deliveries. *Int Wound J* 2019; **16**: 852–859.
- Nakashima M, Chung S, Takahashi A *et al*. A genome-wide association study identifies four susceptibility loci for keloid in the Japanese population. *Nat Genet* 2010; **42**: 768–771.
- Fuentes-Duculan J, Bonifacio KM, Suarez-Farinas M *et al*. Aberrant connective tissue differentiation towards cartilage and bone

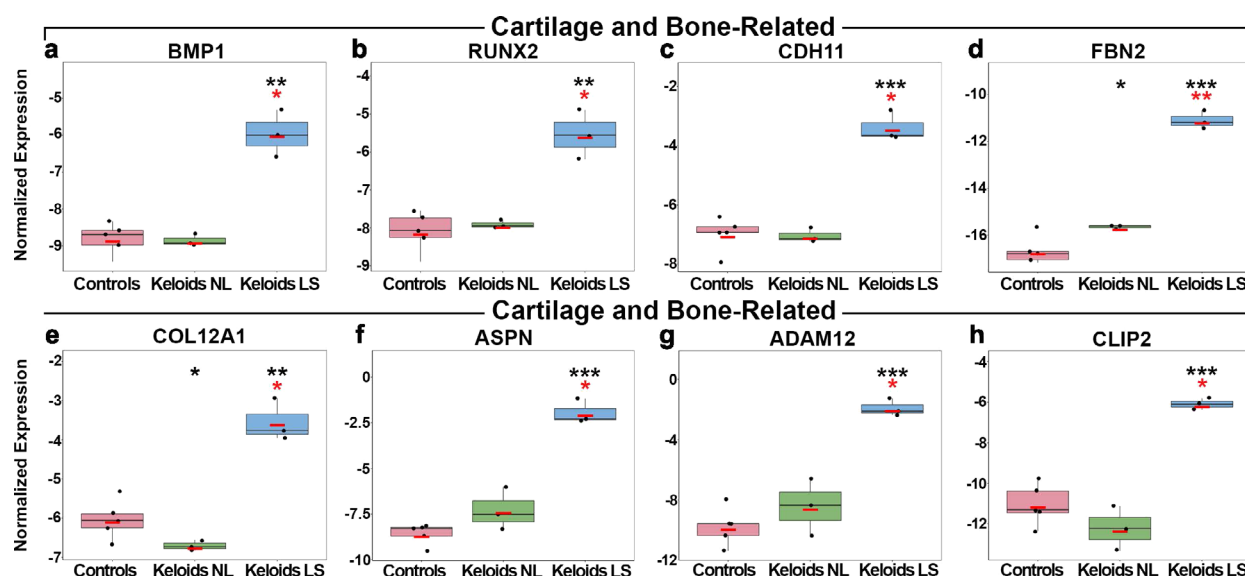


Figure 2 Gene expression of keloid-specific biomarkers. Cartilage and bone-related markers (a–h) measured by quantitative real-time PCR in healthy skin and keloid non-lesional (NL) and lesional (LS) skin. Black stars: significance of comparison between keloid skin and controls; red stars: significance of comparison between lesional versus non-lesional keloid skin. Black lines within boxes represent median values; bold red lines represent mean values. Each black dot represents an individual patient; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

- underlies human keloids in African Americans. *Exp Dermatol* 2017; **26**: 721–727.
- 7 Lu YY, Lu CC, Yu WW *et al*. Keloid risk in patients with atopic dermatitis: a nationwide retrospective cohort study in Taiwan. *BMJ Open* 2018; **8**: e022865.
- 8 Jumper N, Hodgkinson T, Paus R, Bayat A. Site-specific gene expression profiling as a novel strategy for unravelling keloid disease pathobiology. *PLoS ONE* 2017; **12**: e0172955.
- 9 Guttman-Yassky E, Bissonnette R, Ungar B *et al*. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *J Allergy Clin Immunol* 2019; **143**: 155–172.

- 10 Maeda D, Kubo T, Kiya K *et al*. Periostin is induced by IL-4/IL-13 in dermal fibroblasts and promotes RhoA/ROCK pathway-mediated TGF-beta1 secretion in abnormal scar formation. *J Plast Surg Hand Surg* 2019; **53**: 288–294.

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