RESEARCH LETTERS

Identifying new biologic targets in atopic dermatitis (AD): A retrospective histologic analysis

To the Editor: Atopic dermatitis (AD) is a chronic inflammatory disorder associated with significant morbidity in both childhood and adulthood, with increased prevalence and incidence over the past 3 decades.[1] There are limited treatment options for AD, with few addressing pruritus. Pruritogenic mediators, including 5-lipoxygenase, leukotriene B4, interleukin (IL)-2, and matrix metalloproteinase (MMP)-7, have not been characterized within this setting. Furthermore, α-2 macroglobulin, an inflammatory neutralizer, has not been evaluated in AD to our knowledge.[2] Herein we evaluate expression of these factors in AD skin.

This study was approved by the institutional review board at Albert Einstein College of Medicine. Previously biopsied specimens (n = 500) with histologic diagnoses of spongiotic dermatitis were collected. Of those, 40 samples met the following inclusion criteria: (1) clinical diagnosis of AD determined by *International Classification of Diseases, Ninth Revision* code (691.8) and physical

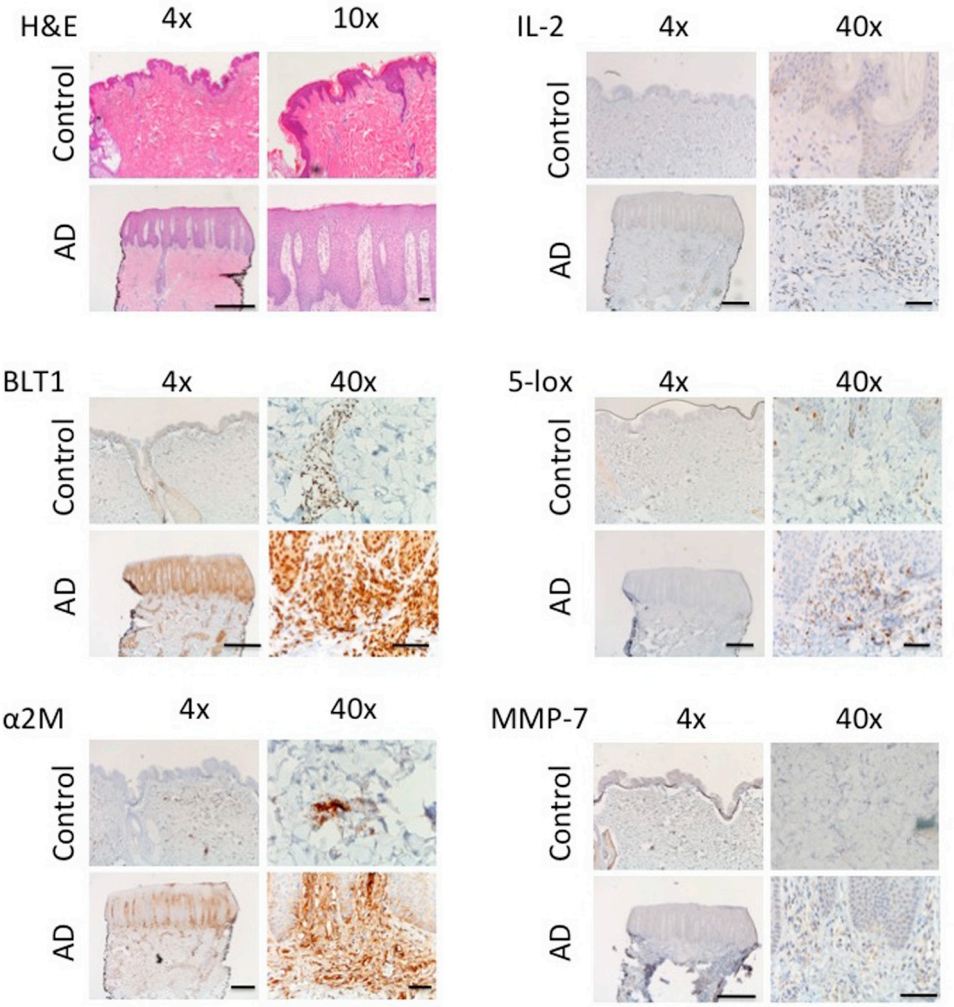


Fig 1. Atopic dermatitis (*AD*) vs control skin: histologic and immunohistochemical staining. Scale bars for hematoxylin-eosin (*H&E*) and interleukin (*IL*)-2 are 500 μm (*left*) and 50 μm (*right*). Scale bars for α-2 macroglobulin (*α2M*), BLT1 (primary receptor for leukotriene B4), 5-lipoxygenase (*lox*), and matrix metalloproteinase (*MMP*)-7 are 500 μm (*left*) and 100 μm (*right*).

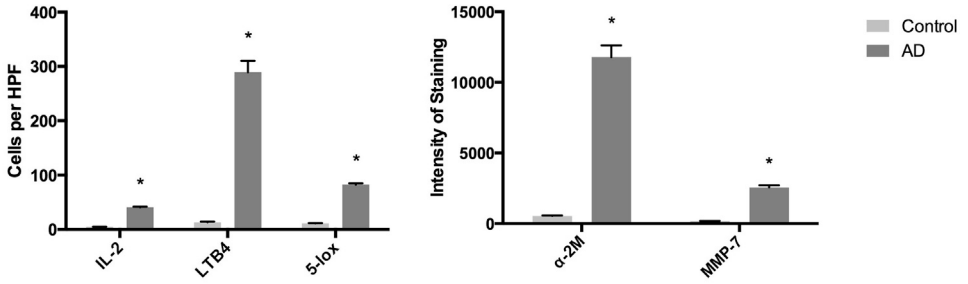


Fig 2. Atopic dermatitis (*AD*) vs control skin: quantitative analysis of skin immunohistochemistry. Data are given as average number of positively staining cells or staining intensity in 10 different high-power fields (*HPF*) for 40 samples per group. Error bars denote SEM. *$P \leq .0001$ in comparing normal-appearing vs AD skin. *IL*, Interleukin; *lox*, lipoxygenase; *LTB4*, leukotriene B4; *MMP*, matrix metalloproteinase; *α-2M*, α-2 macroglobulin.

examination/history; (2) lack of clinically defined contact-allergic/contact-irritant/nummular/autosensitization dermatitis, drug-induced/HIV-associated eczema, or underlying gammopathy; and (3) lack of recent (1 month) immunomodulatory (topical/systemic) treatment. Matched controls (n = 40) were acquired from banked abdominoplasty tissue. Samples were stained with hematoxylin-eosin, immunostained for aforementioned markers, and evaluated with light microscopy. Cell counts and semiquantitative staining intensities were performed.

Mean age of subjects was 37.49 (SD 21.32) years, with 37.5% male and 62.5% female. Biopsy locations included leg (37.5%), arm (22.5%), abdomen (22.5%), back (12.5%), face (2.5%), and chest (2.5%). Duration of lesions ranged 2 to 12 months. Fig 1 illustrates differences between groups. Hematoxylin-eosin showed key features of chronic eczema: compact stratum corneum, acanthotic/spongiotic epidermis, and dermal perivascular lymphocytic infiltrate. Fig 2 shows quantitation of immunostaining. Anti-IL-2 staining revealed statistically significant increases in dermal cellular staining in AD skin compared with controls (40.73 ± 1.269 vs 4.525 ± 0.3453 cells per high-power field; $P \leq .0001$). Both BLT1 (the primary leukotriene B4 receptor 1) and 5-lipoxygenase staining were significantly higher in AD skin than controls (289.5 ± 20.84 vs 12.98 ± 1.305 cells per high-power field; $P \leq .0001$ and 82.53 ± 2.248 vs 10.68 ± 0.7315 cells per high-power field; $P \leq .0001$). MMP-7 staining was significantly higher in AD specimens than controls (2553 ± 150.2 vs 182.4 ± 13.62 relative staining intensity; $P \leq .0001$). Lastly, intensity of α-2 macroglobulin staining was significantly higher in the AD specimens than controls (11,785 ± 833.6 vs 540.3 ± 42.53 relative staining intensity; $P \leq .0001$).

These findings have several implications for AD pathogenesis, and may identify targets to combat inflammation/pruritus. IL-2 is implicated in AD pathophysiology.[3] IL-2 produces pruritus in all patients, a response accelerated in patients with AD.[3] Concurrent with past studies, both pruritogens in the arachidonic acid pathway, leukotriene B4 and 5-lipoxygenase, were increased in AD skin.[4] Inhibition of either mediator mitigates itch in vivo, reinforcing their potential as pharmacologic targets for pruritus in AD.[4]

MMP-7, released during mast cell degranulation, has been implicated in allergic diseases.[5] As mast cells localize to the epidermis in AD skin, their stimulation is associated with increased MMP-7 gene expression.[5] We found elevated MMP-7 in AD skin, reinforcing its potential as a disease marker and therapeutic target. Lastly, α-2 macroglobulin, a ubiquitous protein in serum/tissue that binds/inhibits proteases, growth factors, and cytokines including IL-2, was significantly elevated in lesional AD skin.[2] We hypothesize that this α-2 macroglobulin overexpression results from compensatory amplification of transcription in response to increasing IL-2 and other cytokines in AD.

Our data expose/confirm several mediators and pathways dysregulated in AD skin, which may contribute to pruritus. They may represent targets for modulation of inflammation and pruritus. Interestingly, all mediators investigated are inhibited by hypochlorous acid, formed when sodium hypochlorite (bleach) mixes with water at pH 5 to 7.[2] These results may suggest several new biomarkers in AD that may serve as targets for drugs. Further study may fully elucidate inflammatory mediators and pathways dysregulated in AD.

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Seasonal variation of acne and psoriasis: A 3-year study using the Physician Global Assessment severity scale

To the Editor: Clinicians have observed that psoriasis and acne worsen in the winter and improve in the summer.[1,2] However, studies have predominantly used subjective measures and/or proxies, such as patient-reported severity or clinic visits. We evaluated seasonal variation in psoriasis and acne severity using objective data gathered from the Physician's Global Assessment (PGA; Fig 1).

Demographic data and PGA scores were collected between June 2011 and May 2014 in the New England area. Physicians were trained and billing sheets modified to include psoriasis and acne PGA scales. For seasonality analysis, the year was divided into four 3-month seasons. Chi-square analyses compared seasonal disease clearing ("clear"/"almost clear") and flares ("moderate"/"severe"). To reduce possible bias, we further analyzed disease severity of patients seen ≥2 times over the 3-year interval.

Psoriasis. PGA scores for 5468 psoriasis patients were collected. Sixteen percent of patients were seen in summer, 25% in fall, 31% in winter, and 28% in spring. There were no significant seasonal differences in age or sex. Psoriasis showed summer clearing: 20.4% of patients were graded effectively clear versus 15.3% in winter (Fig 2). When effectively clear patients were compared over 4 seasons, a chi-square test was significant ($P < .01$). Conversely, psoriasis flared in the winter ($P < .01$; Fig 2). Analysis of 3910 psoriasis patients seen multiple times maintained the significant trend of summer clearing ($P < .05$) and winter flaring ($P < .01$).

Acne. PGA scores for 9301 acne patients were collected. Seventy-three percent were women. No significant difference in sex existed between seasons. There was a significant difference in average age at 28.2 years in summer and 30.0 in winter. Eighteen percent of patients were seen in summer, 25% in fall, 28% in winter, and 29% in spring. Acne cleared in the fall: 17.5% of patients were graded effectively clear compared to 13.5% in winter (Fig 2). When effectively clear patients were compared over all 4 seasons, a chi-square test was significant ($P < .01$). Conversely, acne worsened in the winter ($P < .01$; Fig 2). Analysis of 6101 acne patients seen multiple times maintained the significant trend of summer clearing ($P < .01$) and winter worsening ($P < .05$).

Dermatologic clinics were held with equal frequency throughout the year. Fewer psoriasis and acne patients presented to clinic in the summer, perhaps because of disease improvement. It is therefore possible that seasonal differences are even more pronounced.

This study reaffirms that clinical measures can generate data about patient and care delivery outcomes.[3] Mechanistically, winter flaring of psoriasis may be caused by the season's cold temperature, darkness, and low humidity, which can increase skin permeability, epidermal thickening, and stimulate inflammatory mediator production.[2] Its summer improvement may be attributed to the sun's known immunomodulatory and bactericidal effects.[2,4] Similarly, acne's summer/fall improvement may be caused by decreased inflammation from ultraviolet light–induced immune suppression[1] and/or decreasing Langerhans cell reactivity.[5] Although the climate of the northeastern United States may not generalize to regions with less seasonal variation, providers may consider seasonal adjustment of acne plans as they have traditionally done for psoriasis. For example, they may wait until after winter to taper a systemic antibiotic for acne