Atlas of atopic dermatitis

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Ian C. Boothby, BA,[a,b,c] Jeanmarie R. Gonzalez, BA,[b] and Tiffany C. Scharschmidt, MD[c] *San Francisco, Calif*

Key words: *Atopic dermatitis, scRNAseq, fibroblasts, T cells, dendritic cells, COL6A5*

Atopic dermatitis (AD) is a common inflammatory skin disease, often of early-life onset, for which the prevalence continues to increase in industrialized countries. Its pathogenesis is complex, with disease progression driven by a combination of factors, including genetic susceptibility, altered skin microbiota, and immune perturbations.[1] AD has been historically categorized as a disease of type 2 inflammation, but recent work has identified a range of AD endotypes with mixed T_H1, T_H2, T_H17, and T_H22 characteristics.[1,2] Epidermal barrier dysfunction is both a key predisposing factor and a consequence of AD. Activated keratinocytes augment tissue inflammation via production of cytokines, chemokines, costimulatory molecules, and pattern recognition receptors.[3] Neurons perpetuate the itch-scratch cycle and can also directly activate skin immune-cell subsets.[4] Clinical manifestations of AD thus derive from intricate communication between multiple immune and nonhematopoietic skin cell types (Fig 1), many of which remain poorly defined and challenging to simultaneously quantify with traditional tools.

Previous studies have attempted to comprehensively define the molecular basis of AD using bulk RNA sequencing and microarray profiling. However, nuanced cellular-level biology may be lost in aggregate quantification of gene expression. In this issue, He et al[5] present analysis of single-cell RNA sequencing (scRNAseq) data from lesional and nonlesional skin from adult subjects with AD along with that of healthy controls. By using the 10X chromium droplet–based platform, they sequence approximately 39,000 cells, far more than possible by lower throughput plate-based single-cell assays. The resulting data set is both comprehensive (ie, all major cell types represented) and robust (ie, reflects multiple biological replicates). In many cases, the results confirm recognized features of AD pathogenesis while adding further molecular detail. For instance, epidermal hyperplasia and abnormal differentiation of lesional AD skin manifest as a cluster of keratinocytes with enhanced expression of proliferation markers (*UBEC, TOP2A*) and wound healing–associated keratins (*KRT1, KRT10*). Single-cell analysis of the cutaneous immune infiltrate confirmed enrichment of $CD4^+$ T_H2 cells in AD lesions, as well as the presence of other T_H subsets producing IL-22 and IL-26. This adds to a growing body of evidence that the inflammatory phenotype of AD is more mixed than previously appreciated.[2]

Perhaps the greatest power of scRNAseq is the potential for discovery of new cell types by unbiased transcriptomic clustering. Indeed, the major novel finding by He et al is that of a previously undescribed population of $COL6A5^+$ fibroblasts in lesional AD skin. The accumulation of $COL6A5^+$ fibroblasts was validated by immunofluorescence microscopy, which demonstrated localization near the dermal-epidermal junction. An additional fibroblast population enriched for *MFAP5* and *FBN1* transcripts was also elevated in both lesional and nonlesional AD as compared with healthy skin. Computational alignment of their sequencing data to that from previous studies of human skin stromal cell populations allowed the authors to further verify that $COL6A5^+$ and $MFAP5^+$ fibroblasts are absent in healthy tissue. How specific these populations are to AD versus other cutaneous disease states will require further investigation.

Fibroblasts and other stromal cell populations remain relatively understudied because of a lack of clearly distinguishing cell surface markers, a high degree of cellular plasticity, and challenges associated with preserving their *in vivo* phenotype during *ex vivo* culture.[6] Despite this, stromal cells have been identified as clear pathogenic drivers of inflammatory disease. For example, in rheumatoid arthritis, they are thought to help recruit immune cells, nucleate ectopic lymphoid structures, and contribute directly to tissue damage.[7] The advent of scRNAseq has fueled renewed interest in dissecting stromal heterogeneity in human tissues and disease states. Although not studied to date in AD, fibroblasts are known to drive AD-like keratinocyte differentiation *in vitro* as well as to secrete cytokines, chemokines, and extracellular matrix following T_H2 stimulation.[8,9] The high level of CCL-19, IL-32, and periostin expression detected among $COL6A5^+$ AD fibroblasts in this study suggests a distinct proinflammatory potential. Intriguingly, work in the last year has provided mechanistic *in vivo* evidence that lung and adipose tissue fibroblasts directly support the persistence and activation of tissue-resident type 2 lymphocytes.[10] It is thus intriguing to speculate that stromal support of skin-resident immune cells may mediate T_H2 persistence in AD lesions and underlie disease recurrence and chronicity. These studies pave the way for further mechanistic work aimed at dissecting the contribution of these fibroblast subsets to AD pathogenesis.

One important technical note is that the 10X scRNAseq platform is limited to approximately 10,000 cells per sample. He et al conducted scRNAseq on whole-tissue skin digests, a strategy that favors comprehensive acquisition of all major cell types at the expense of deep interrogation of rare populations. Focused follow-up studies that use presorting and subsequent single-cell sequencing of populations of interest may identify yet other novel cell subsets enriched in AD skin. Although the cohort assembled by He et al is robust by contemporary standards of scRNAseq studies of human tissues, the sample size of 5 subjects

From [a]the Medical Scientist Training Program, [b]the Biomedical Sciences Program, and [c]the Department of Dermatology, University of California San Francisco, San Francisco.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication March 10, 2020; accepted for publication March 27, 2020.

Available online April 25, 2020.

Corresponding author: Tiffany C. Scharschmidt, MD, 513 Parnassus Ave, HSW1201H, San Francisco, CA 94143. E-mail: Tiffany.Scharschmidt@ucsf.edu.

J Allergy Clin Immunol 2020;145:1558-9.

0091-6749/$36.00

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https://doi.org/10.1016/j.jaci.2020.03.040

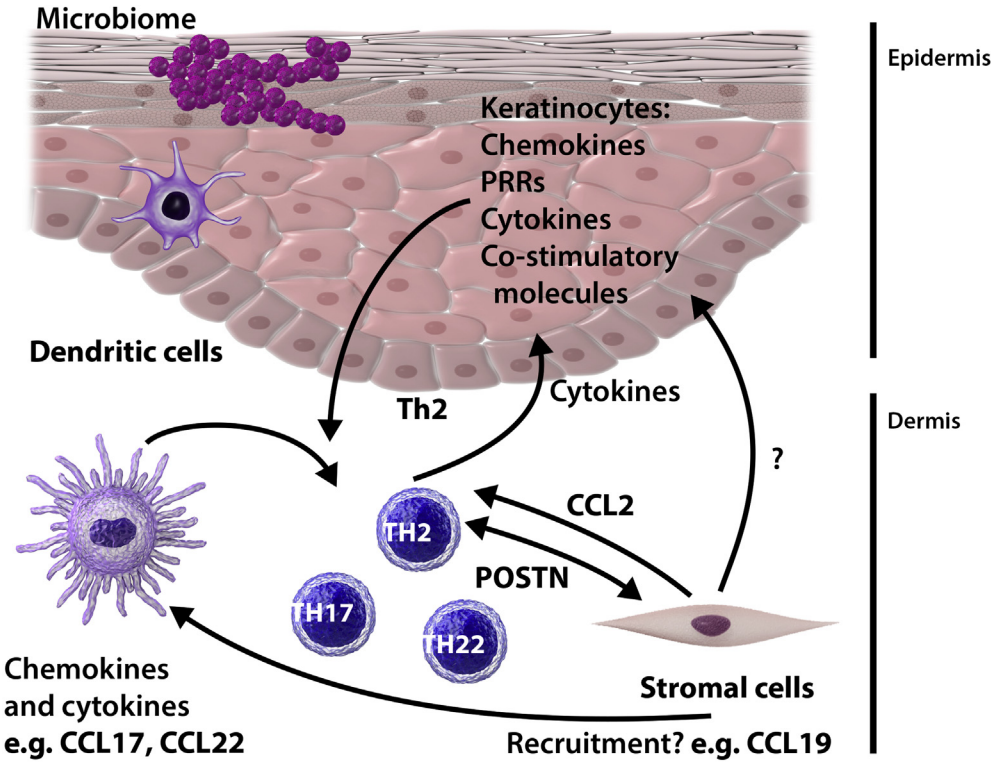


FIG 1. Potential role of novel fibroblast population in AD pathogenesis. AD results from complex multicellular interactions in the skin of affected individuals. Keratinocytes express various factors, which act on immune cells to drive inflammation. Dendritic cells produce cytokines and chemokines that drive T-cell responses (eg, CCL17, and CCL22 in He et al). T cells produce cytokines that in turn feed back onto keratinocytes. In line with evidence for proinflammatory roles of stromal cells in other diseases, data from He et al indicate that *COL6A5*$^{+}$ and *MFAP5*$^{+}$ fibroblasts may contribute to AD pathogenesis by CCL-19–mediated recruitment of dendritic cells via CCL19 and/or potentiation of T_H2 and T_H22 responses via CCL2 and POSTN. *POSTN*, Periostin; *PRR*, pattern recognition receptor.

with AD is still small given the known clinical diversity of AD presentation. Genetics, immune phenotype, and serum IgE levels are a few of the various factors defining the spectrum of known AD endotypes. Further single-cell analyses from expanded cohorts of patients, including pediatric samples, may help elucidate differential drivers of disease pathogenesis among endotypes by correlating inflammatory-cell subsets with changes in the cellular composition and transcriptional state of the skin. The findings of He et al thus represent an important first step toward a comprehensive and detailed single-cell definition of AD, paving the way for discoveries that may yield insights into disease pathogenesis and treatment.

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