RNA sequencing atopic dermatitis transcriptome profiling provides insights into novel disease mechanisms with potential therapeutic implications

Background: Genomic profiling of lesional and nonlesional skin of patients with atopic dermatitis (AD) using microarrays has led to increased understanding of AD and identification of novel therapeutic targets. However, the limitations of microarrays might decrease detection of AD genes. These limitations might be lessened with next-generation RNA sequencing (RNA-seq).

Objective: We sought to define the lesional AD transcriptome using RNA-seq and compare it using microarrays performed on the same cohort.

Methods: RNA-seq and microarrays were performed to identify differentially expressed genes (criteria: fold change, ≥2.0; false discovery rate ≤0.05) in lesional versus nonlesional skin from 18 patients with moderate-to-severe AD, with real-time PCR (RT-PCR) and immunohistochemistry used for validation.

Results: Both platforms showed robust disease transcriptomes and correlated well with RT-PCR. The common AD transcriptome identified by using both techniques contained 217 genes, including inflammatory (S100A8/A9/A12, CXCL1, and 2′-5′-oligoadenylate synthetase-like [OASL]) and barrier (MKi67, keratin 16 [K16], and claudin 8 [CLDN8]) AD-related genes. Although fold change estimates determined by using RNA-seq showed somewhat better agreement with RT-PCR (intraclass correlation coefficient, 0.57 and 0.70 for microarrays and RNA-seq vs RT-PCR, respectively), bias was not eliminated. Among genes uniquely identified by using RNA-seq were triggering receptor expressed on myeloid cells 1 (TREM-1) signaling (eg, CCL2, CCL3, and single immunoglobulin domain IL1R1 related [SIGIRR]) and IL-36 isoform genes. TREM-1 is a surface receptor implicated in innate and adaptive immunity that amplifies infection-related inflammation.

Conclusions: This is the first report of a lesional AD phenotype using RNA-seq and the first direct comparison between platforms in this disease. Both platforms robustly characterize the AD transcriptome. Through RNA-seq, we unraveled novel disease pathology, including increased expression of the novel TREM-1 pathway and the IL-36 cytokine in patients with AD.