

Letter to the Editor

Residual genomic signature of atopic dermatitis despite clinical resolution with narrow-band UVB

To the Editor:

Atopic dermatitis (AD) is one of the most common inflammatory skin diseases and is characterized by barrier defects and altered immune activation. Narrow-band UVB (NB-UVB) phototherapy has emerged as an effective treatment for patients with moderate-to-severe AD. We recently showed that resolution of clinical AD with NB-UVB treatment is associated with suppression of inflammatory pathways and reduction of epidermal hyperplasia.¹ However, AD lesions tend to recur in the same locations after treatment, suggesting that residual cellular and molecular alterations might predispose to new lesions. Gene expression profiling of psoriasis lesions treated with etanercept for 3 months demonstrated that resolution of clinical disease to nonlesional levels was associated with residual expression of a subset of disease-related genes, termed the residual disease genomic profile

(RDGP).² Likewise, identifying the set of AD genes that do not improve to nonlesional and normal skin levels is important for understanding the residual structural and functional alterations in the skin and their therapeutic implications.^{2,3}

We analyzed the residual genomic and histologic changes in clinically resolved lesions of 11 patients with moderate-to-severe AD treated with NB-UVB 3 times weekly for up to 12 weeks.¹ For comparison with normal skin, we also obtained biopsy specimens from 10 healthy volunteers (see the **Methods** section in this article's Online Repository at www.jacionline.org). Our study aimed to identify the RDGP, as defined by genes with less than 75% improvement in the AD transcriptome (the differentially expressed genes between lesional and nonlesional skin).

RT-PCR and immunohistochemistry data of the cohort of patients treated with NB-UVB demonstrated significant suppression of the majority of inflammatory genes and cells ($P < .05$ for post vs pre paired comparisons), as determined by decreases in mRNA gene expression and cell counts, respectively (see **Table E1** in this article's Online Repository at www.jacionline.org). Epidermal hyperplasia, as measured based on epidermal thickness

TABLE I. Selected AD genes that have less than 75% improvement with NB-UVB

Symbol	Description	Week 12 vs week 0 (LS)*	Week 0 (LS vs NL)†	Improvement (%)
Upregulated genes that have <75% improvement				
<i>CXCL2</i>	Chemokine (C-X-C motif) ligand 2	-0.06	0.82	7.73
<i>CXCL1</i>	Chemokine (C-X-C motif) ligand 1	-0.20	1.72	11.75
<i>ABHD5</i>	Abhydrolase domain containing 5	-0.08	0.62	13.42
<i>CCR1</i>	Chemokine (C-C motif) receptor 1	-0.70	1.20	58.81
<i>CCR7</i>	Chemokine (C-C motif) receptor 7	-0.99	1.58	62.65
<i>MMP1</i>	Matrix metalloproteinase 1 (interstitial collagenase)	-2.34	3.35	69.79
<i>GJB2</i>	Gap junction protein, β 2, 26 kDa	-0.87	1.18	73.90
<i>IL8</i>	IL-8	-2.42	3.28	73.96
<i>SOCS3</i>	Suppressor of cytokine signaling 3	-1.39	1.86	74.45
Downregulated genes that have <75% improvement				
<i>S100B</i>	S100 calcium binding protein B	-0.90	-0.97	-92.82
<i>LEP</i>	Leptin	-0.43	-2.69	-15.85
<i>AQP7</i>	Aquaporin 7	-0.12	-0.95	-12.78
<i>LGALS12</i>	Lectin, galactoside-binding, soluble, 12	-0.22	-1.82	-12.24
<i>DGAT2</i>	Diacylglycerol O-acyltransferase homolog 2 (mouse)	-0.08	-1.85	-4.32
<i>LPL</i>	Lipoprotein lipase	0.00	-2.45	-0.13
<i>PPARG</i>	Peroxisome proliferator-activated receptor γ	0.17	-1.84	9.47
<i>ELOVL5</i>	ELOVL family member 5, elongation of long-chain fatty acids	0.13	-1.33	9.48
<i>FASN</i>	Fatty acid synthase	0.26	-1.70	15.18
<i>RBP4</i>	Retinol binding protein 4, plasma	0.48	-2.79	17.25
<i>GYG2</i>	Glycogenin 2	0.42	-2.14	19.56
<i>RARRES2</i>	Retinoic acid receptor responder (tazarotene induced) 2	0.20	-0.97	20.37
<i>AOC3</i>	Amine oxidase, copper containing 3 (vascular adhesion protein 1)	0.21	-0.95	22.41
<i>FABP4</i>	Fatty acid binding protein 4, adipocyte	0.32	-1.43	22.63
<i>ANGPT1</i>	Angiopoietin 1	0.25	-0.92	27.09
<i>RBP7</i>	Retinol binding protein 7, cellular	0.35	-1.02	34.48
<i>FADS3</i>	Fatty acid desaturase 3	0.38	-1.07	35.62
<i>THRSP</i>	Thyroid hormone responsive (SPOT14 homolog, rat)	1.83	-4.09	44.64
<i>ALDH1A1</i>	Aldehyde dehydrogenase 1 family, member A1	0.64	-1.26	50.59
<i>BTC</i>	Betacellulin	1.34	-2.45	54.89
<i>FABP7</i>	Fatty acid binding protein 7, brain	1.88	-3.33	56.42
<i>CLDN8</i>	Claudin 8	1.02	-1.76	57.94

LS, Lesional; NL, nonlesional.

*Log₂(FCH) for treatment effect at week 12 versus baseline LS value.

†Log₂(FCH) for the clinical phenotype defined as LS versus NL baseline values.

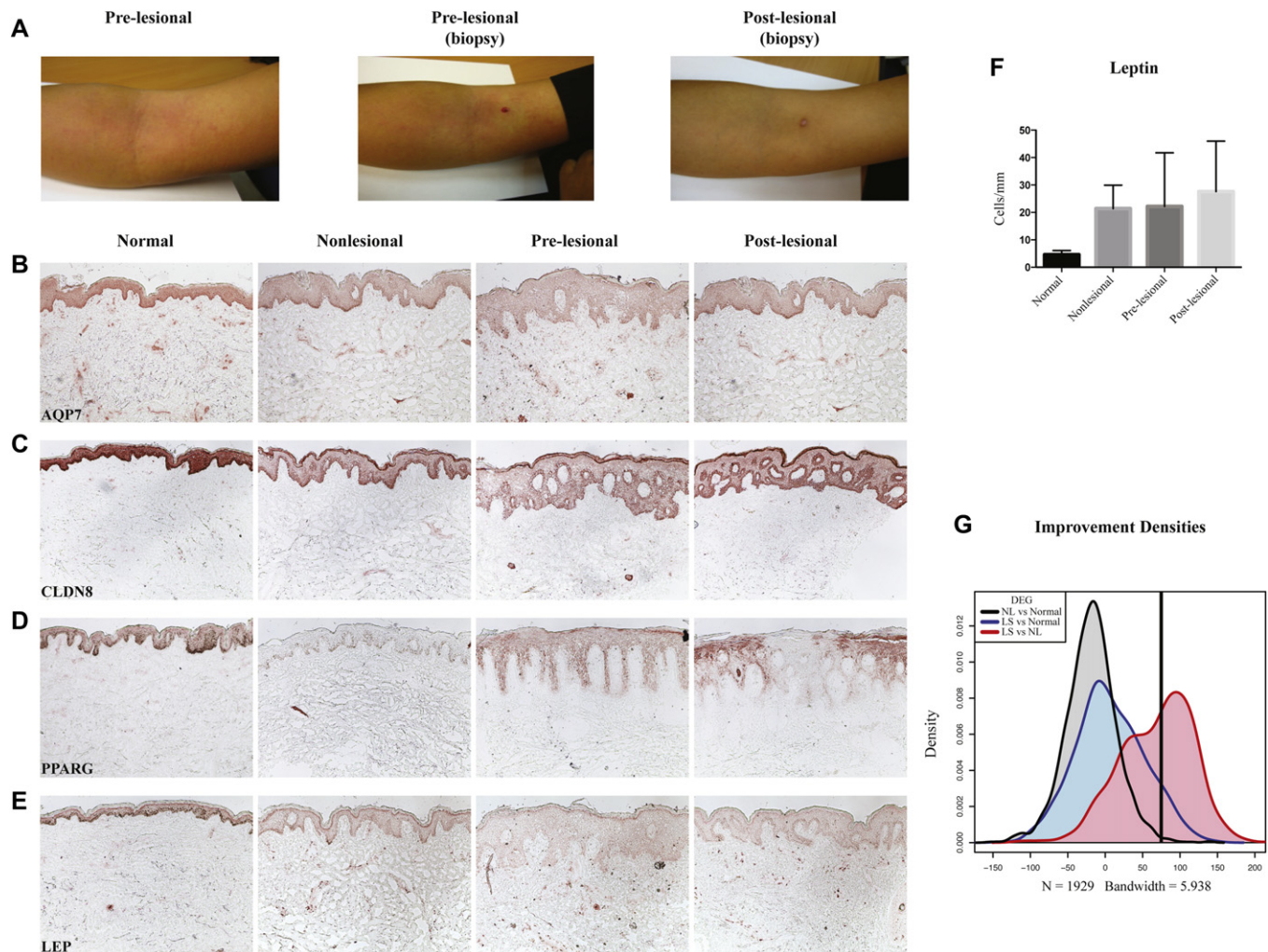


FIG 1. Clinical improvement of AD lesions contrasts with residual histologic and genomic disease. **A**, Representative images demonstrating clinical improvement in AD lesions with NB-UVB treatment. **B-E**, Representative staining in normal, nonlesional, and lesional skin specimens before and after NB-UVB treatment, all demonstrating lack of improvement compared with normal skin. Scale bar = 100 μ m. **F**, Cell counts of leptin demonstrate increased dermal expression of leptin in AD lesional and nonlesional skin compared with normal skin, which did not improve with treatment. **G**, A significant percentage of the distribution of improvement density of lesional skin compared with nonlesional skin includes genes that show an improvement of greater than 75%, with the peak near 100%, whereas the distribution of the improvement density of lesional skin and nonlesional skin compared with normal skin is far less than 75% improvement, with both peaks near 0. DEG, Differentially expressed genes; LS, lesional; NL, nonlesional.

and Ki67 cell counts, improved by 88% and 118%, respectively. RT-PCR results also showed improvement in the majority of inflammatory markers with only 3 inflammatory genes lacking 75% improvement, including myxovirus-resistance 1 (*MX1*), *S100A7*, and *S100A8* (range, 53% to 73%). Similarly, the majority of inflammatory cells dramatically improved, including CD3⁺ and CD8⁺ T cells (105% improvement), CD83⁺ mature dendritic cells (DCs; 117% improvement), CD1a⁺ Langerhans cells (154% improvement), CD206⁺ inflammatory dendritic epidermal cells (341% improvement), and eosinophils (516% improvement). However, CD11c⁺ myeloid DCs and FcεRI⁺ inflammatory dendritic epidermal cells improved by only 53% and 59%, respectively. Thus although there is major improvement in epidermal pathology and inflammatory markers, which is consistent with our previously reported data,¹ there is residual inflammation that might initiate new lesions.

We then analyzed the residual genomic changes in clinically resolved AD lesions, as defined by changes in the AD transcriptome with treatment, to determine the RDGP. Many immune genes, such as *CD2*, granzyme B, *IL2RG*, *S100A7*, *IL7R*, and *CCL18*, improved by greater than 98% (see Table E2 in this article's Online Repository at www.jacionline.org). In addition, many structural and proliferation genes, such as keratins 6A and 16, late cornified envelope 3D, *WNT5A*, cyclins (B1, B2, and E2), and *Ki67* demonstrated improvement. However, 115 up-regulated and 243 downregulated probe sets (73 upregulated and 171 downregulated genes) from the AD transcriptome showed less than 75% improvement (RDGP threshold <75%, Table I). Inflammatory genes that did not improve include angiopoietin 1 (*ANGPT1*), *CXCL2*, *CXCL1*, *CCR1*, *CCR7*, and *IL8*, which are involved in leukocyte chemotaxis. Additionally, structural genes that lacked improvement include aquaporin 7 (*AQP7*),

claudin 8 (*CLDN8*), leptin (*LEP*), and peroxisome proliferator-activated receptor γ (*PPARG*), with the latter 2 known to have important roles in lipid metabolism and immune activation.

To determine functional sets of genes that were altered with NB-UVB, we measured the average improvement for canonical pathways using the Gene Set Enrichment Analysis software from the Molecular Signatures Database (see Table E3 in this article's Online Repository at www.jacionline.org). Pathways with less than 75% improvement include the cytokine and cytokine receptor interaction and chemokine receptor pathways, which improved by 67% and 58%, respectively. The PPAR signaling pathway, which is involved in lipid signaling, cellular proliferation and differentiation, and inflammatory responses, improved by only 30%.

We further detected lack of improvement in selected structural genes through immunohistochemical staining (Fig 1, B-E), which contrasts with the clinical resolution of AD lesions (Fig 1, A). Levels of AQP7, an aquaglyceroporin similar to AQP3, an important determinant of epidermal hydration,⁴ are decreased in AD lesions and do not return to normal levels with treatment (Fig 1, B). *CLDN8*, a tight junction protein, also lacks improvement (Fig 1, C). Tight junction proteins (ie, claudin 1) are downregulated in patients with AD, contribute to barrier dysfunction, and inversely correlate with T_H2 activation.⁵ *PPARG*, which has emerged as an important structural element with reduced expression in patients with AD and a functional negative immune regulator of DCs in the onset of AD,⁶ does not improve to normal levels (Fig 1, D). Leptin, another structural protein primarily involved in lipid metabolism, shows decreased epidermal expression and increased dermal cellular expression that did not return to normal levels (Fig 1, E-F). Leptin is a known pleiotropic cytokine that binds to its receptor on all immune cells, upregulates adhesion molecules, induces release of cytokines and chemokines, and stimulates proliferation and survival of various immune cells.⁷ The reduced epidermal leptin might have no effect on the skin, as suggested by transgenic mice studies,⁸ or could potentially contribute to increased fatty acid oxidation in the epidermal barrier, whereas the increased dermal expression (Fig 1, F) likely promotes immune activation after treatment.

Lesions with clinical resolution after NB-UVB treatment maintain a residual genomic disease phenotype, with incomplete suppression of inflammatory mediators and residual structural and lipid abnormalities (Table I) contributing to persistent epidermal deficits. This RDGP should be considered in the development of AD treatments. For example, the concomitant use of *PPARG* activators (ie, thiazolidinediones), which have demonstrated efficacy in AD,⁹ could be considered. Although some of these residual changes might be specific to NB-UVB treatment, which has known effects on keratinocytes,¹⁰ it is crucial to define and compare RDGP across various therapeutic agents. It is important to note, as seen in Fig 1, G, that although lesional AD skin significantly improved compared with nonlesional skin, both lesional and nonlesional skin demonstrate minor improvement compared with normal skin (see Tables E4 and E5 in this article's Online Repository at www.jacionline.org), representing a "background"

phenotype that must also be considered in the development of AD therapeutics. Without specifically targeting background skin, as well as the RDGP of AD, lesions will likely continue to recur after treatment.

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MATERIALS AND METHODS

Patients

Pre-treatment and post-treatment lesional AD and nonlesional (≥ 10 cm from any active lesion) AD skin biopsy specimens and blood samples were obtained from a total of 12 patients with moderate-to-severe chronic AD under an institutional review board-approved protocol.^{E1} Patients received full-body NB-UVB 3 times weekly until clearance or up to 12 weeks. Patients were allowed to use emollients only with no additional pharmacologic treatment during the study period. Biopsy specimens were obtained from the same skin area to evaluate therapeutic effect. The patients' characteristics and clinical, genomic and histologic responses were previously published, as determined by analyses of their skin biopsies.^{E1} Patients were included if there was at least 50% reduction in SCORAD and defined as "responders" if there was more than 40% reduction in pathologic epidermal thickness, which determined the power of the study.^{E1} The 11 responders' data were reanalyzed in this study. The present study is a subgroup analysis of previous gene expression data.^{E1, E2} For comparisons with normal skin, we also obtained biopsies from 10 healthy volunteers (7 females and 3 males; age range: 26-74, mean age: 46.5) under an institutional review board-approved protocol.

Gene expression data

RNA from skin biopsies of 12 patients was hybridized to Affymetrix HGU133APlus2.0 chips (Affymetrix, Santa Clara, CA), which were used as previously described.^{E3} Microarray data is deposited in the National Center for Biotechnology Information's Gene Expression Omnibus (series accession no. GSE27887).

Statistical analysis

In a prior publication,^{E1} a linear mixed-effect model with group as the fixed effect and a random intercept for each patient in the framework of Bioconductors' limma package was used to model gene expression using interaction time x response and to account for the paired structure of lesional and nonlesional skin and pre- to post- NB-UVB measures. From this model, the treatment effect at 12 weeks was estimated for responders using the limma package.

AD clinical signature (lesional vs nonlesional), background signature (nonlesional vs normal) and lesional vs normal genes were analyzed at the end of treatment to evaluate lesional return to nonlesional skin and, nonlesional return to normal skin and lesional return to normal skin, respectively. For each disease gene, we quantified improvement after 12 weeks of treatment as:

$$\text{Improvement in clinical signature} = 100 \times \left(\text{sign}(X_{12} - X_{NL}) \right) \times \frac{X_{12} - X_{LS}}{X_{12} - X_{NL}}$$

$$\text{Improvement in background signature} = 100 \times \left(\text{sign}(X_{NL} - X_N) \right) \times \frac{X_{12} - X_{NL}}{X_{NL} - X_N}$$

$$\text{Improvement in lesional vs normal} = 100 \times \left(\text{sign}(X_{12} - X_N) \right) \times \frac{X_{12} - X_{LS}}{X_{12} - X_N}$$

in which X_{LS} , X_{NL} , X_N , and X_{12} are the $\log_2$ expression values at lesional, nonlesional, normal and 12 weeks of treatment, respectively. RDGP is defined as the genes with improvement below 75%.

We included the canonical pathways (C2 CP) using GSEA software from Molecular Signatures Database (MSigDB, <http://www.broadinstitute.org/gsea/msigdb>).

Reverse transcriptase PCR and immunohistochemistry

Skin biopsies for T cell and dendritic cell markers were stained and counted and RT-PCR was carried out as previously reported.^{E1} Most of these results were previously published^{E1} and are reanalyzed here to determine mean improvement after 12 weeks of treatment. Standard procedures were followed for immunohistochemistry using purified mouse anti-human monoclonal and rabbit anti-human polyclonal antibodies:

Antibody	Vendor	Clone	Isotype	Dilution
Claudin-8	GeneTex	Polyclonal	IgG	1:200
Aquaporin-7	Bioss	Polyclonal	IgG	1:100
PPAR γ	Santa Cruz	Monoclonal (E-8)	IgG ₁	1:200
Leptin	Abcam	Monoclonal (BDI142)	IgG _{2a}	1:500

Biotin-labeled horse anti-mouse antibody and goat anti-rabbit antibody (Vector Laboratories, Burlingame, Calif) were amplified with avidin-biotin complex (Vector Laboratories) and developed with chromogen 3-amino-9-ethylcarbazole (Sigma-Aldrich, St Louis, Mo). All immunostained sections were photographed and analyzed with ImageJ analysis to measure epidermal thickness and cell counts per millimeter (ImageJ 1.42). Immunohistochemistry was conducted in batches for paired samples and representative staining is shown. RT-PCR reaction was performed with EZ-PCR Core Reagents (Life Technologies, Carlsbad, Calif).

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Table E1. Improvement of RT-PCR data and cell counts with NB-UVB

	LS-NL	POST-PRE	% Improvement
<i>Epidermis</i>			
Thickness	159.08	-139.97	87.98
Ki67 cell counts	34.00	-40.00	117.65
K16 mRNA	2.62	-1.54	58.59
<i>Genes</i>			
<i>Th2</i>			
IL13	2.58	-2.00	77.24
CCL11	0.54	-0.45	83.87
CCL17	1.82	-1.56	85.86
CCL18	2.57	-2.66	103.63
IL10	0.73	-0.77	105.34
CCL22	1.96	-2.30	117.50
CCL5	1.12	-1.33	117.97
<i>Th1</i>			
MX1	0.99	-0.56	56.38
IFN γ	1.28	-1.20	93.78
<i>Th17</i>			
IL17A	0.98	-0.78	79.78
IL23p19	1.04	-1.00	96.70
IL23p40	0.49	-0.49	100.17
<i>Treg</i>			
FOXP3	0.75	-0.73	97.10
<i>Terminal Differentiation</i>			
CDSN	0.54	-0.93	171.26
<i>IL22</i>			
S100A7	2.28	-1.20	52.74
S100A8	1.21	-0.88	73.11
IL22	1.14	-1.50	135.08
<i>Cells</i>			
CD11c (myeloid DCs)	46.56	-24.44	52.51
FcϵRI (IDECs)	71.78	-42.22	58.82
<i>TRAIL (inflammatory DCs)</i>	43.43	-34.14	78.62
<i>CD1c (resident DCs)</i>	31.33	-25.56	81.56
<i>BDCA-2 (plasmacytoid DCs)</i>	20.00	-18.21	91.07
<i>OX40L (atopic DCs)</i>	27.57	-25.29	91.71
<i>CD3 (T cells)</i>	214.78	-225.67	105.07
<i>CD8 (cytotoxic T cells)</i>	33.71	-35.43	105.08
<i>CD1b (IDECs)</i>	21.75	-24.38	112.07

<i>CD83 (mature DCs)</i>	4.14	-4.86	117.24
<i>CD1a (LCs, IDECs)</i>	43.88	-67.63	154.13
<i>CD206 (IDECs, macrophages)</i>	17.71	-60.43	341.13
<i>MBP (eosinophils)</i>	0.86	-4.43	516.67

RT-PCR LS-NL data are presented as log₂ and cell counts data are presented as the differences in thickness or cell counts. Abbreviations: BDCA2, blood dendritic cell antigen 2; CDSN, corneodesmosin; DC, dendritic cells; FcεRI, Fc receptor for IgE; FOXP3, forkhead box protein 3; IDEC, inflammatory dendritic epidermal cell; K16, keratin 16; LS, lesional; MBP, major basic protein; MX1, myxovirus-resistance 1; NL, nonlesional; OX40L, OX40 ligand; TRAIL, TNF-related apoptosis-inducing ligand. Bold values indicate genes that had an improvement of <75%.

Table E2. Selected atopic dermatitis genes that have >75% improvement with NB-UVB

Symbol	Description	W12 vs W0 (LS)	W0 (LS vs NL)	% Improvement
Upregulated genes that have >75% improvement				
CD2	CD2 molecule	-1.94	1.47	131.58
SERPINB13	serpin peptidase inhibitor, clade B (ovalbumin), member 13	-2.16	1.69	127.63
CCNB2	cyclin B2	-1.24	1.02	122.19
S100A7	S100 calcium binding protein A7	-1.59	1.41	113.28
IL7R	interleukin 7 receptor	-1.69	1.53	110.44
KRT6A	keratin 6A	-1.18	1.07	110.24
ITK	IL2-inducible T-cell kinase	-1.90	1.80	105.50
MMP12	matrix metalloproteinase 12 (macrophage elastase)	-3.26	3.10	104.98
RAB27A	RAB27A, member RAS oncogene family	-1.05	1.00	104.85
CD69	CD69 molecule	-1.12	1.08	103.68
CCL18	chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)	-2.78	2.72	102.04
LTB	lymphotoxin beta (TNF superfamily, member 3)	-1.35	1.33	101.45
CCNB1	cyclin B1	-1.07	1.06	101.15
IL2RG	interleukin 2 receptor, gamma (severe combined immunodeficiency)	-0.87	0.89	98.01
WNT5A	wingless-type MMTV integration site family, member 5A	-1.13	1.16	97.99
OAS3	2'-5'-oligoadenylate synthetase 3, 100kDa	-1.35	1.39	97.12
LCE3D	late cornified envelope 3D	-2.49	2.58	96.57
CCNE2	cyclin E2	-1.12	1.19	94.10
LCK	lymphocyte-specific protein tyrosine kinase	-1.61	1.72	93.10

GZMB	granzyme B (granzyme 2, cytotoxic T-lymphocyte-associated serine esterase 1)	-2.14	2.33	91.74
LCP2	lymphocyte cytosolic protein 2 (SH2 domain containing leukocyte protein of 76kDa)	-0.92	1.01	91.10
MKI67	antigen identified by monoclonal antibody Ki-67	-1.48	1.63	90.48
S100A9	S100 calcium binding protein A9	-2.19	2.43	89.98
SERPINB3	serpin peptidase inhibitor, clade B (ovalbumin), member 3	-2.38	2.72	87.58
KRT16	keratin 16	-1.79	2.06	86.99
CDK5R1	cyclin-dependent kinase 5, regulatory subunit 1 (p35)	-0.94	1.09	85.65
CDCA2	cell division cycle associated 2	-1.03	1.21	85.25
S100A7A	S100 calcium binding protein A7A	-2.64	3.12	84.55
OASL	2-5-oligoadenylate synthetase-like	-1.76	2.08	84.46
PI3	peptidase inhibitor 3, skin-derived	-1.79	2.13	84.14
JAK3	Janus kinase 3	-0.99	1.24	79.99
CCNA2	cyclin A2	-0.83	1.06	78.66
IRF7	interferon regulatory factor 7	-1.00	1.31	76.21
IL1F9	interleukin 1 family, member 9	-1.39	1.84	75.50
SELE	selectin E	-2.31	3.06	75.24
CCL19	chemokine (C-C motif) ligand 19	-0.95	1.27	75.20
Downregulated genes that have >75% improvement				
CGNL1	cingulin-like 1	1.37	-0.97	141.57
RYR3	ryanodine receptor 3	0.94	-0.92	102.89
NOSTRIN	nitric oxide synthase trafficker	0.92	-0.91	101.92

Abbreviations: LS, lesional; NL, nonlesional; W, week.

Table E3. Resolution of canonical pathways at the end of NB-UVB treatment

Name	Mean improvement	n	Selected genes in pathway
ST_T_CELL_SIGNAL_TRANSDUCTION	135.13	5	RASGRP1, PTPRC, ITK, LCP2, LCK
REACTOME_CYCLIN_A1_ASSOCIATED_EVENTS_DURING_G2_M_TRANSITION	122.64	6	CDC2, CCNB2, CCNB1
REACTOME_SIGNALING_IN_IMMUNE_SYSTEM	113.02	15	CD47, CD2, ITK, IRF7, MMP1, ANGPT1, C7
REACTOME_CELL_CYCLE_CHECKPOINTS	101.06	16	MCM4, CDC20, MCM4, CCNE2, CHEK1, MCM10
KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY	58.37	7	PRKAA2, PPARGC1A, SOCS3, ACACB, LEP
REACTOME_CHEMOKINE_RECEPTORS_BIND_CHEMOKINES	58.07	6	CCL19, CCR7, IL8, CCR1, CXCL1, CXCL2
REACTOME_METABOLISM_OF_LIPIDS_AND_LIPOPROTEINS	31.37	23	SGPP2, HSD11B1, GPD1, FASN, ABHD5, PLIN1
KEGG_PPAR_SIGNALING_PATHWAY	29.86	14	ACADL, NR1H3, SORBS1, FABP4, PPARG, AQP7
KEGG_GLYCEROLIPID_METABOLISM	-2.41	8	MGLL, DGAT2, LPL, GPAM

n=number of genes in pathway.