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ORIGINAL RESEARCH

Reanalysis of microarray data reveals insights into altered transcriptional activity of T helper 17 and regulatory T cell signaling in psoriasis

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Abstract: Identifying differential expression of genes in psoriatic and healthy skin by microarray data analysis is a key approach to understand the pathogenesis of psoriasis. Analysis of more than one dataset to identify genes commonly upregulated reduces the likelihood of false positives and narrows down the possible signature genes. Genes controlling the critical balance between T helper 17 and regulatory T cells are of special interest in psoriasis. Our objectives were to identify genes that are consistently upregulated in lesional skin from three published microarray datasets. We carried out a reanalysis of gene expression data extracted from three experiments on samples from psoriatic and nonlesional skin using the same stringency threshold and software and further compared the expression levels of 92 genes related to the T helper 17 and regulatory T cell signaling pathways. We found 73 probe sets representing 57 genes commonly upregulated in lesional skin from all datasets. These included 26 probe sets representing 20 genes that have no previous link to the etiopathogenesis of psoriasis. These genes may represent novel therapeutic targets and surely need more rigorous experimental testing to be validated. Our analysis also identified 12 of 92 genes known to be related to the T helper 17 and regulatory T cell signaling pathways, and these were found to be differentially expressed in the lesional skin samples.

Keywords: psoriasis, gene array analysis, gene expression profiling

Introduction

Psoriasis is a common, chronic, inflammatory, relapsing skin disease mediated by T cells, dendritic cells, and several inflammatory cytokines.[1,2] Recent advances in our knowledge of mechanisms linking innate and adaptive immunity have led to reconsideration of the roles of key players in the pathogenesis of the disease with many uncertainties.[3]

Studies of gene expression profiling provide valuable insights into the pathomechanisms involved in psoriasis. The transcriptome from skin biopsies was previously analyzed on microarrays using the 7,000-oligonucleotide array HU6800, the approximately 12,600 element array U95A, the approximately 63,000 probe sets Affymetrix U95A–E arrays, and cDNA arrays.[4–7] As a result, a number of changes in gene and/or protein expression have been detected in psoriasis, eg, interleukin (IL)-1 and tumor necrosis factor alpha (TNF-α), which were reported to be upregulated with subsequent activation of the NF-κB pathway.[5] It was also noted that Wnt5a and other genes involved in the Wnt signaling pathway are differentially expressed in psoriatic plaques. However, their functional contribution to the pathophysiology of psoriasis needs to be elaborated.[8] Recently, concerns regarding false positives and/or missing

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key signals from microarray data have arisen due to the large size of the data output, the background noise inherent in the technology, and the financial constraints on the number of replicates.[9] As a result, reanalysis of published microarray data has become a useful extension of the technology.

Recent studies have shown the crucial role of the T helper 17 (T_H17) cell population in development of the disease.[10] T_H17 cells are activated by the dendritic cell cytokine IL-23, can produce IL-17, IL-22, and TNF-α, and have many other downstream proinflammatory effects.[11] Conversely, T regulatory (T_{Reg}) cells suppress effector T cell responses and prevent their potentially pathogenic effects.[12] T_{Reg} cells are characterized by expression of the transcription factor Forkhead box P3. Differentiation of both T_H17 and T_{Reg} cells can require transforming growth factor-beta, and the balance between these cells may be mediated by IL-6. The production of IL-6 during inflammatory reactions makes Forkhead box P^+ T_{Reg} nonfunctional and allows effector cells to induce inflammation in the target organ.[13,14] However, much remains to be elucidated concerning the relationship between proinflammatory and regulatory cells.[10]

This study aims to comprehensively reanalyze microarray gene expression data extracted from three different experiments deposited in the GEO datasets,[8,15,16] according to the same criteria. All experiments included skin biopsies from lesional and nonlesional skin, while only two experiments include additional samples from healthy control skin. By reporting genes that are found to be upregulated as a result of the disease in more than one experiment, the possibility of false positives is reduced and the output gene list is refined. We also related our findings to the expression profile of 92 genes (Table 1) involved in the T_H17 and T_{Reg} regulatory pathways.

Table 1 Genes involved in the T helper 17 and regulatory T cell signaling pathways that were specifically interrogated in our analysis

Surface molecules	CD28, CD34, CD3D, CD3E, CD3G, CD4, CD25, CD127, CD40LG, CD8A, ICAM1, ICOS, ISG20, CTLA4
Chemokines	CCL1, CCL2, CCL20, CCL22, CCL7, CD247, CX3CL1, CXCL1, CXCL12, CXCL2, CXCL5, CXCL6, IL8, MMP13, MMP3, MMP9, CCR4, CCR6
Cytokines	CSF2, CSF3, IFNG, IL10, IL12B, IL13, IL15, IL17A, IL17C, IL17D, IL17F, IL18, IL1A, IL1B, IL2, IL21, IL22, IL23A, IL25, IL27, IL3, IL4, IL5, IL6, TGFB1, TNFA, TNFB
Cytokine receptors	IL12RB1, IL12RB2, IL17RB, IL17RC, IL17RD, IL17RE, IL23R, IL6R, IL7R
Signaling pathway molecules and transcriptional factors	CACYBP, CEBPB, CLEC7A, EDG1, FOXP3, GATA3, JAK1, JAK2, NFATC2, NFKB1, RORC, SOCS1, SOCS3, STAT3, STAT4, STAT5A, STAT6, SYK, TBX21, TIRAP, TLR4, TRAF6, YY1, T-BET

Materials and methods

Gene microarray experiments

Data from three experiments with GEO accession numbers, GSE6710, GSE13355, and GSE14905, were extracted from the free PubMed domain (http://www.ncbi.nlm.nih.gov/gds?term=psoriasis) for further analysis. The GSE6710 experiment[8] includes data from lesional and nonlesional skin samples from 13 individuals with psoriasis and used parent platform GPL96 Affymetrix Human Genome U133A GeneChip® (Affymetrix, Santa Clara, CA, USA). In the GSE13355 experiment,[15] the parent platform GPL570 Affymetrix Human Genome U133 PLUS 2.0 GeneChip was used and a total of 180 skin samples were profiled, encompassing biopsies from the healthy skin of 64 control subjects and biopsies from the involved and uninvolved skin of 58 patients with psoriasis. In the GSE14905 experiment,[16] the parent platform GPL570 Affymetrix Human Genome U133 Plus 2.0 GeneChip was used and a total of 82 skin samples were profiled (21 normal, 28 uninvolved skin, and 33 lesional skin).

Microarray data analyses

Data files from the above experiments were analyzed with GeneSpring GX11 software (Agilent Technologies, Santa Clara, CA, USA). Ambiguous samples (three samples from GSE6710 and one sample from each of GSE13355 and GSE14905) were excluded by running quality control on each dataset. The data were filtered by expression within the 20–100th percentile, log-transformed, normalized using the Robust Multichip Average algorithm, and baseline converted to the median of all samples. Differential expression in lesional versus nonlesional skin samples was compared using paired Student's *t*-test statistics with a *P*-value cutoff ≤ 0.05 and a fold change ≥ 2.0. To discern further the biological meaning of the output gene lists, we functionally annotated significantly expressed genes on human Kegg pathways using Database for Annotation, Visualization and Integrated Discovery (DAVID)[17] version 6.7 and the HT Human Genome U133 Plus set as background.

For identification of possible interactions between genes of potential importance for the development of psoriasis, network analysis was performed with NetBox 1.0 (cBio, Memorial Sloan-Kettering Cancer Center, New York, NY, USA) (http://cbio.mskcc.org/tools/netbox/netbox.tar.gz). This tool uses human interactions derived from literature-

curated data sources for prediction of interaction of genes in a submitted gene list. NetBox is preloaded with a human interaction network derived from four literature-curated data sources, including the Human Protein Reference Database,[18] Reactome,[19,20] NCI-Nature Pathway Interaction Database,[21] and Memorial Sloan-Kettering Cancer Center Cancer Cell Map, and provides the netAnalyse.py method for network analysis, which was described by Cerami et al[22] in 2010. The netAnalyse.py method settings applied during analysis were shortest path threshold =1 and *P*-value threshold =0.05. The resultant networks were then imported into Cytoscape for further editing and analysis.[23]

Results

Reanalysis of three published microarray datasets[8,15,16] revealed a number of probe sets that are differentially expressed (upregulated and/or downregulated) in psoriatic lesional versus nonlesional skin from each experiment, and the Venn diagram in Figure 1 illustrates the intersections between the three experiments. In general, a total of 73 probe sets representing 57 genes were found common to the three datasets and were significantly upregulated in the psoriatic lesions (Figure 1, with a complete list in Tables S1 and S2). Of these probe sets, only 26 representing 20 genes have no previous reported link to the etiopathogenesis of psoriasis (Table S2).

We then studied the transcriptional activity underlying the dynamic interplay between the $CD4^+$ T_H17 and $CD4^+CD25^{high}FoxP3^+T_{Reg}$ cell lineages in the skin of psoriatic patients from the three above experiments. This interplay has recently been linked to the etiopathogenesis of psoriasis and some other autoimmune diseases.[10,24]

A list of 92 genes (Table 1) that are likely to be involved in the T_H17 and T_{Reg} signaling pathways was prepared. In the first instance, we searched for the differential expression of these genes in the three experiments.

A total of 12 genes were found to be differentially expressed (upregulated/downregulated) in the lesional skin samples with a false discovery rate of <0.01 and an absolute fold change >2 in at least one of the datasets (Tables 2–4). In the data extracted and analyzed from the GSE6710 experiment,[8] five probe sets representing four genes were found to be differentially expressed in the psoriatic lesions, with CD34 being the only example to be downregulated (Table 2). The corresponding profile for the data from GSE13355[15] is a total of nine probe sets/genes that are all upregulated in the lesional versus nonlesional skin (Table 3). In the GSE14905 dataset,[16] a total of 12 probe sets representing 11 genes were found to be significantly upregulated in the lesional versus nonlesional skin (Table 4).

Network analysis was performed on the significantly changed genes reported in Tables 2–4, S1, and S2. Genes associated with T_H17/T_{Reg} reported in Table 1 were added to this list to aid identification of a possible connection between these genes. The resultant network was then imported into Cytoscape for further analysis.[23] In order to depict possible interactions between genes reported in Tables 2–4, S1, and S2, the nodes for these genes in the network were enlarged and were colored orange, red (upregulated in psoriasis), or green (downregulated in psoriasis). Identified direct interactions of these genes, which were predicted by the network analysis, were marked as connecting red lines between these nodes (Figure 2).

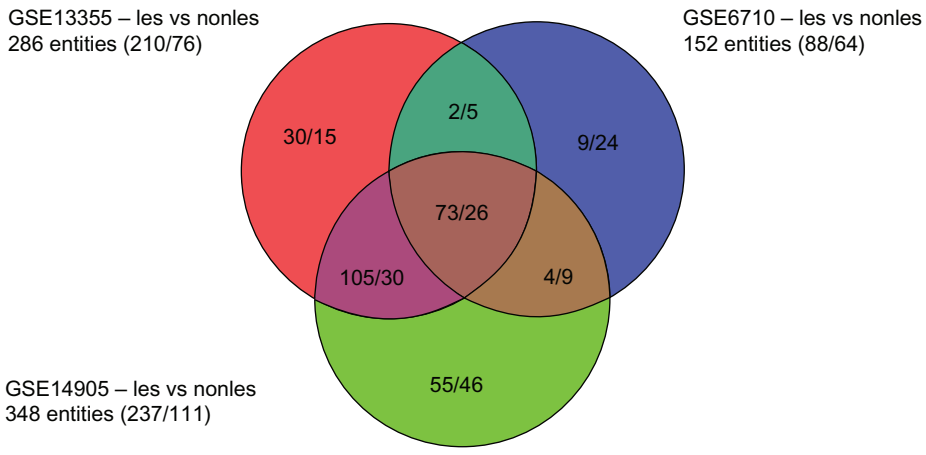

Figure 1 Venn diagram illustrates the number of probe sets that show significant higher expression/number of those showing significant lower expression in lesional versus nonlesional skin from the three experiments, ie, GSE6710 (upper right circle), GSE13355 (upper left circle), and GSE14905 (lower circle). The intersecting regions represent probe sets that are common in the specific experiments.
Abbreviations: GSE, GeneSys Export file; les, lesional; vs, versus; nonles, nonlesional.

Table 2 Fold changes (log_2 transformed) and corrected *P*-values (calculated by GeneSpring GX) for genes involved in the T helper 17 and regulatory T cell signaling pathways and upregulated and/or downregulated

Probe ID	Gene symbol	Gene description	Lesional versus nonlesional	
			Log_2 fold change	Corrected *P*-value
208991_at	STAT3	Signal transducer and activator of transcription 3	1.229	2.84E-05
208992_s_at	STAT3	Signal transducer and activator of transcription 3	1.469	4.07E-07
209543_s_at	CD34	Cluster of differentiation 34	−1.046	1.67E-05
202859_x_at	IL8	Interleukin 8	2.686	1.17E-05
205476_at	CCL20	C-C motif ligand 20	1.932	7.39E-07

Notes: Positive and negative values of fold changes indicate upregulation and downregulation, respectively. Data were extracted and analyzed from the GSE6710 experiment.[8]

Network analysis was also performed on significant differentially expressed genes in each of the three data sets investigated, ie, GSE6710, GSE14905, and GSE13355 (significant = two-fold upregulated/downregulated in lesional versus nonlesional skin with a false discovery rate <0.05).

Table 3 Fold changes (log_2 transformed) and corrected *P*-values (calculated by GeneSpring GX) for genes involved in the T helper 17 and regulatory T cell signaling pathways and upregulated and/or downregulated

Probe ID	Gene symbol	Gene description	Lesional versus nonlesional	
			Log_2 fold change	Corrected *P*-value
208992_s_at	STAT3	Signal transducer and activator of transcription 3	1.132	1.02E-28
39402_at	IL1B	Interleukin 1 beta	1.104	9.79E-23
205476_at	CCL20	C-C motif ligand 20	2.889	2.99E-35
205798_at	IL7R	Interleukin 7 receptor	1.266	6.91E-16
207861_at	CCL22	C-C motif chemokine 22	1.032	7.31E-25
209774_x_at	CXCL2	Chemokine C-X-C motif ligand 2	1.831	1.27E-24
211506_s_at	IL8	Interleukin 8	2.582	2.64E-17
216598_s_at	CCL2	Chemokine C-C motif ligand 2	1.436	1.95E-18
203936_s_at	MMP9	Matrix metallopeptidase 9	1.486	6.18E-29

Notes: Positive and negative values of fold changes indicate upregulation and downregulation, respectively. Data are extracted and analyzed from the GSE13355 experiment.[15]

Table 4 Fold changes (log_2 transformed) and corrected *P*-values (calculated by GeneSpring GX) for genes involved in the T helper 17 and regulatory T cell signaling pathways and upregulated and/or downregulated

Probe ID	Gene symbol	Gene description	Lesional versus nonlesional	
			Log_2 fold change	Corrected *P*-value
208991_at	STAT3	Signal transducer and activator of transcription 3	1.169	4.17E-15
208992_s_at	STAT3	Signal transducer and activator of transcription 3	1.247	1.04E-13
39402_at	IL1B	Interleukin 1 beta	1.191	5.86E-09
205758_at	CD8A	Cluster of differentiation 8a	1.001	3.51E-11
202859_x_at	IL8	Interleukin 8	3.606	5.22E-11
205476_at	CCL20	C-C motif ligand 20	2.664	4.69E-15
205798_at	IL7R	Interleukin 7 receptor	2.012	1.03E-12
207861_at	CCL22	C-C motif chemokine 22	1.210	4.22E-10
209774_x_at	CXCL2	Chemokine C-X-C motif ligand 2	1.870	7.91E-12
216598_s_at	CCL2	Chemokine C-C motif ligand 2	1.345	2.62E-07
213539_at	CD3D	T cell surface glycoprotein CD3 delta chain	1.282	3.04E-11
203936_s_at	MMP9	Matrix metallopeptidase 9	1.600	3.96E-11

Notes: Positive and negative values of fold changes indicate upregulation and downregulation, respectively. Data are extracted and analyzed from the GSE14905 experiment.[16]

Nodes in these networks were colored according to fold change (green downregulated, yellow-orange-red upregulated) and size of the node indicates relative significance (larger being more significant) (Figures S1–S3).

Discussion

This study confirmed previously reported and newly identified changes in gene transcription in psoriatic skin that might contribute to the etiopathogenesis. Our approach was to reanalyze the microarray raw data deposited in the GEO datasets from three different experiments.[8,15,16] Simple comparison of the available published differentially expressed genes from these studies was avoided. This was to ensure consistent analyses rather than rely on different statistical tests and to enforce the same stringency threshold.[25,26] The use of data extracted from more than one experiment filters out false positives and narrows down the list of genes that show a significantly

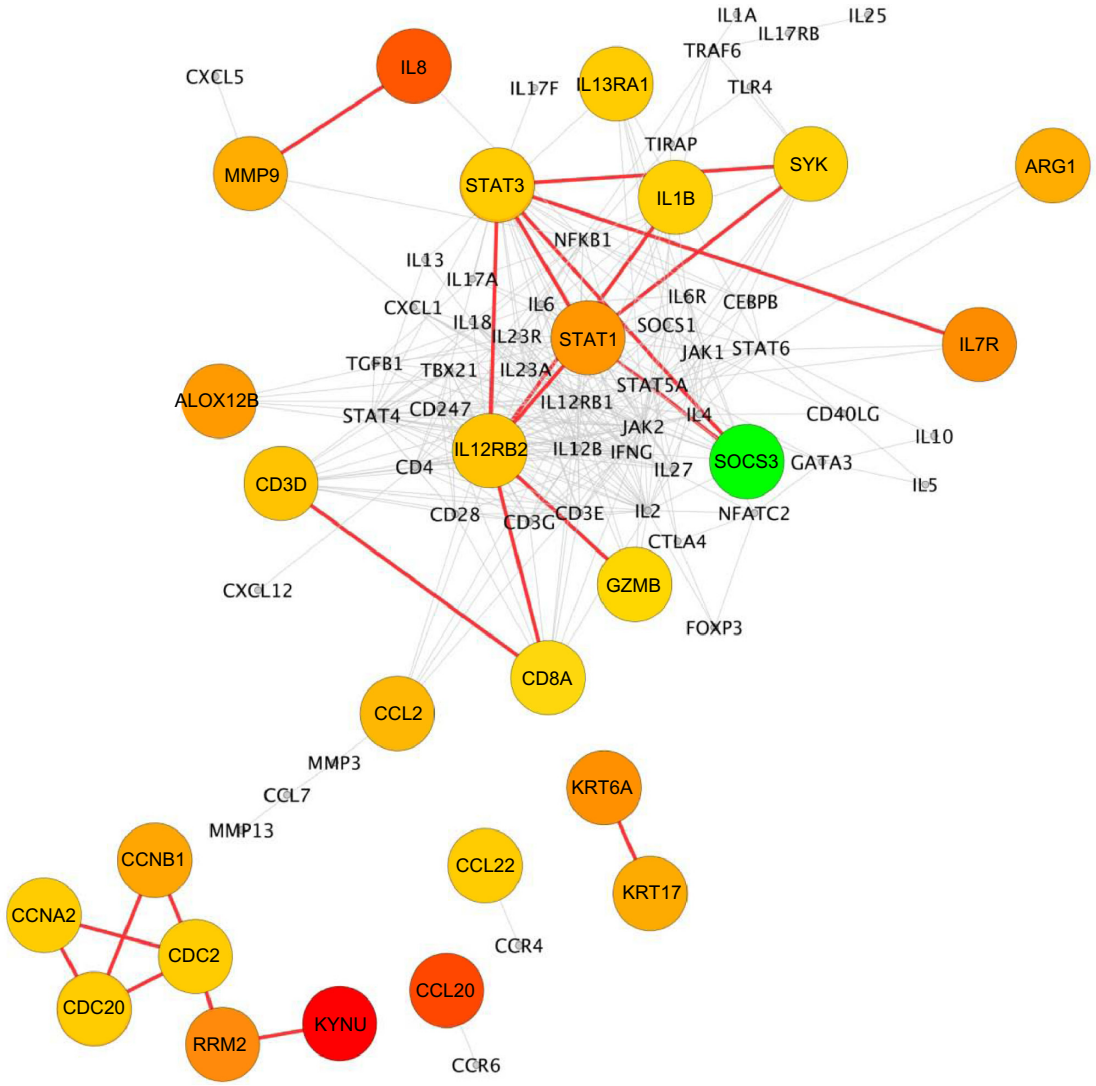

Figure 2 Network analysis (netAnalyse.py method, setting shortest path threshold =1 and *P*-value threshold =0.05) shows possible interaction between the potential gene targets for treatment of psoriasis as identified in this study. Green circles indicate downregulated genes, orange/red circles indicate upregulated genes and small gray circles indicate part of the T helper 17/regulatory T cell pathway, but were not found to be affected in the experiments analyzed in this study. Lines between nodes show known direct interactions between genes. The network was edited in Cytoskape, with a force-directed layout applied. Nodes showing affected genes were enlarged and direct interactions between these nodes were highlighted in red to highlight the relevant interactions identified in this analysis in the context of the T helper 17/regulatory T cell pathway.

altered expression level as a result of the disease. Moreover, it decreases the chance of drawing incorrect conclusions because the data are not generated from one laboratory. In 2005, Irizarry et al[27] demonstrated that there are relatively large differences in data obtained from different laboratories, even between those using the same platform, but the results from the best performing laboratories agree rather well.

Genes that show significant overexpression in psoriatic skin were functionally annotated on human Kegg pathways (Tables S1 and S2). These genes need further investigation with other techniques and may provide insights into pathogenesis or novel therapeutic targets.

In effect, and despite many efforts, the network of genes that shows significantly altered expression in psoriasis and represents the molecular signature of the disease is still inconspicuous. This is manifested by the relatively high number of recent studies that focused on reanalysis of published data as well as designing new experiments. In 2009, Gudjonsson et al[28] reported some transcriptional differences between uninvolved skin from psoriatic patients as opposed to skin from normal individuals. Cluster analysis of transcripts with significantly altered expression identified a group of genes involved in lipid metabolism with highly correlated gene expression. Their results suggest decreased lipid biosynthesis and increased innate immunity in uninvolved psoriatic skin.

In 2010, the same group[29] performed a gene expression study of 58 paired lesional and uninvolved psoriatic and 64 control skin samples. Comparison of involved psoriatic and

normal skin identified new differentially regulated transcripts. Enriched gene ontology categories included immune response, defense response, and keratinocyte differentiation. In 2012, Tian et al[30] adopted a statistically-based meta-analytic approach, which combines the results of individual studies to overcome the problem of having different lists of differentially expressed genes across experiments due to variations introduced in the microarray pipelines. Their method differs from our approach since we have not combined the disparate microarray studies to derive a single estimate of the overall differential expression level for each gene. Instead, we reanalyzed each individual experiment using the same tools and criteria and listed the differentially expressed genes found in common to overcome the problem of getting false positives. The list of differentially expressed genes found in common is a limited set, and in particular, is limited only to genes featured on the less comprehensive array platform (GPL96 Affymetrix Human Genome U133A GeneChip). Combining data from different experiments into one pool is confounded by the inherent differences in platforms and probe sets and the effects of laboratory conditions. Further, our approach was notably different from others in that we extended our search to test a clinical hypothesis that altered transcriptional activity of the genes controlling the active interplay between T_H17 and T_{Reg} cells is important in disease expression.

This contemporary paradigm for psoriasis is supported by other recent studies. Krueger et al[31] investigated the effect that neutralization of the T_H17 cell cytokine, IL-17, has on the clinical features of psoriasis using quantitative real-time polymerase chain reaction and microarrays. Their results suggest that IL-17 is a key "driver" cytokine that activates pathogenic inflammation in psoriatic subjects. They also highlighted that neutralizing IL-17 with the anti-IL-17 monoclonal antibody, ixekizumab, might be a successful therapeutic strategy in psoriasis.[31] Concomitantly, two studies[32,33] have been published in which the gene expression signature was used to stratify lesions and reveal distinct molecular subgroups within the clinical phenotype of plaque psoriasis. This is a new direction that will be very important in developing personalized medication for chronic disease.

Our study is also focused on expression of the genes underlying the balance between T_H17 and T_{Reg} cells. Signal transducer and activator of transcription (STAT3, a member of the JAK-STAT signaling pathway), and the chemokines IL-8 and chemokine (C-C motif) ligand 20 (CCL20) were found to be upregulated in the three experiments. These results are in accordance with previously published data.[34–36] Recently, Miyoshi et al[37] showed that use of STA-21, a small STAT3 inhibitor, was useful in ameliorating psoriatic skin lesions, not only in K5.Stat3C transgenic mice but also in humans. These results emphasize the importance of targeting STAT3 in the quest for new treatments of psoriasis. Similarly, ABX-IL8 is a fully human IgG_2 monoclonal antibody that binds to human IL-8 with high affinity and specificity and is currently in Phase II clinical investigation for treatment of psoriasis by Abgenix (Fremont, CA, USA).[38] Strikingly, Kim et al[39] found that pretreatment with fluvastatin and simvastatin inhibited migration of human $CD4^+$T cells towards CCL20 in a chemotaxis migration assay. These findings suggest that these drugs may be of benefit in alleviating psoriasis via interrupting the CCL20/chemokine receptor 6 (CCR6) chemotactic interaction, thus inhibiting infiltration of T_H17 cells.

Other chemokines known to be related to T_H17 and T_{Reg} signaling pathways and found to be differentially upregulated in lesional skin samples in at least one of the three experiments are CCL2, CCL22, chemokine (C-X-C motif) ligand 2 (CXCL2), and matrix metallopeptidase 9 (MMP9). CCL2 is expressed by keratinocytes in both atopic dermatitis and psoriasis and when stimulated with TNF-α and/or interferon gamma (IFN-γ) in a dose-dependent manner.[40] CCL2 binds to the chemokine receptor CCR2 on monocytes and macrophages. CCR2 is overexpressed in monocytes from patients with psoriasis and atopic dermatitis. Thus, CCL2 and CCR2 interaction is likely to be of importance for monocyte/macrophage trafficking.

CCL22 also belongs to the C-C motif family and is synthesized and secreted by macrophages, dendritic cells, and osteoclasts. It acts selectively on chronically activated lymphocytes by interacting with the CCR4 receptor. Traditionally, CCR4 has been reported to be expressed preferentially on T cells belonging to the Th2 subpopulation. Recent studies have also shown expression of CCR4 on T_H17 cells as well as on T_{Reg} cells.[41] The macrophage-derived chemokine/CCL22 was found to be elevated in the synovial fluid of patients with rheumatoid arthritis and psoriatic arthritis, suggesting that CCR4 could play a role in attracting skin-specific memory T cells to the joints.[42]

MMP9 belongs to a family of proteolytic enzymes that are capable of degrading all components of the extracellular matrix, a key event in the development of cartilage destruction and joint erosion, and may play a part in psoriatic arthritis. In 2006, Cordiali-Fei et al[43] observed that MMP9 was decreased, along with clinical improvement in the lesional skin and sera of psoriatic patients receiving infliximab, the anti-TNF-α monoclonal antibody. MMP9 may directly sustain the

inflammatory process and tissue destruction or contribute by allowing the traffic of inflammatory cells and enhancing the activity of inflammatory cytokines.

CXCL2 was reported to increase by two-fold in psoriatic versus atopic dermatitis skin.[44] Bowcock and Cookson[44] proposed that the higher expression of chemokines in psoriasis is among other factors that could sustain chronic T cell activation and persistence within focal skin regions.

Interestingly, our analysis did not show that all genes relating to the T_H17 network (listed in Table 1) are differentially expressed in lesional skin. In another similar study[26] where comparison of the expression of psoriasis-related genes across four different studies was conducted, some well recognized inflammatory genes involved in psoriasis, for example, IFN-γ, IL-17, and inducible nitric oxide synthase, were not detected. Using separate polymerase chain reaction, the authors showed that this may be due to low amplification of these genes on the Affymetrix gene array platform (0–4 range of expression in $\log_2$ scale), and hence fold change is not accurately measured. As a positive control, this false negative finding suggests caution in interpreting gene array data. Most analysis pipelines filter out low abundance genes so they may be excluded from the statistical analysis, or the resultant fold change is very low, albeit significant. This is a major limitation of the use of these arrays for the study of these genes. Another possible explanation is that the expression was measured in bulk skin samples containing numerous cell types, and most of these genes are expressed in multiple cell types, so upregulation of a certain gene in one cell type may be neutralized by downregulation in another cell type.[32]

CD34, CD3D, and CD8A are the only surface receptor genes from the list in Table 1 that were found to be differentially expressed in psoriatic lesions. CD34 was found in one experiment to be downregulated in lesional versus nonlesional skin (Table 2).

In our analysis, both CD3D and CD8A were found to be upregulated in lesional versus nonlesional skin. Both genes were previously reported to be downregulated in patients responding to alefacept, the LFA3-Ig fusion protein that binds to CD2.[45]

Other genes upregulated in our analysis (listed in Table 1) are IL-1β and IL-7R. In a previous study,[46] IL-1β was easily detectable by immunofluorescence microscopy and found to be localized predominantly in epidermal keratinocytes. Immunoreactive IL-1β was found to be elevated in cytosolic extracts derived from involved psoriatic keratomes relative to keratomes of normal skin. The elevated IL-1β protein was accompanied by elevated levels of IL-1β mRNA in psoriatic skin relative to normal skin. IL-7R expression is also known to increase by at least a two-fold magnitude in the peripheral blood cells of psoriatic patients when measured by cDNA microarray technology.[47]

Conclusion

Studies of gene expression profiling have the potential to greatly improve our understanding of the physiologic and molecular mechanisms underlying the pathogenesis and progression of psoriasis. However, the high chance of getting false positives has become a concern. Reanalysis of data extracted from different experiments using the same software and stringent criteria could reduce this risk and thus refine the list of proposed new therapeutic targets. Our study also highlights the altered expression of genes known to be involved in the control of the T_H17/T_{Reg} balance in psoriatic skin. By reanalyzing repository data and specifically querying these pathways, we provide further evidence that this balance is of key importance in the etiopathogenesis and progression of psoriasis and demonstrate another approach to mining this data.

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Disclosure

The authors declare that they have no competing interests in this work.

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Supplementary materials

Table S1 Probe sets for genes previously reported to have a role in pathogenesis of psoriasis and found to be upregulated in the lesional versus nonlesional skin samples from each of the three experiments, ie, GSE6710, GSE13355, and GSE14905

Probe ID	Gene Symbol	Gene title	Functional annotation on human Kegg pathways	GSE6710 Lesional versus nonlesional		GSE13355 Lesional versus nonlesional		GSE14905 Lesional versus nonlesional		Reference
				Log_2 fold change	Corrected *P*-value	Log_2 fold change	Corrected *P*-value	Log_2 fold change	Corrected *P*-value	
200887_s_at	STAT1	Signal transducer and activator of transcription 3	Chemokine signaling pathway, Toll-like receptor signaling pathway, JAK-STAT signaling pathway, pathways in cancer, pancreatic cancer	1.072	2.55E-05	1.501	3.51E-41	1.685	1.08E-16	Yao et al[21]
209969_s_at	STAT1	Signal transducer and activator of transcription 3	Chemokine signaling pathway, Toll-like receptor signaling pathway, JAK-STAT signaling pathway, pathways in cancer, pancreatic cancer	1.874	1.81E-17	2.819	1.24E-39	2.458	1.41E-16	Yao et al[21]
201695_s_at	NP	Purine nucleoside phosphorylase	Purine metabolism, pyrimidine metabolism, nicotinate and nicotinamide metabolism	1.419	6.84E-07	1.986	4.66E-34	1.678	7.18E-15	Morris and Omura[1]
202069_s_at	IDH3A	Isocitrate dehydrogenase subunit alpha	Citrate cycle	1.348	2.82E-06	1.388	1.15E-33	1.025	4.66E-11	Romanowska et al[2]
202345_s_at	FABP5	Fatty acid-binding protein	PPAR signaling pathway	1.372	2.56E-06	1.284	0	1.534	3.45E-16	Madsen et al[3]
202357_s_at	C2/CFB	complement component 2 (C2) and complement factor B	Complement and coagulation cascades	1.037	4.60E-05	2.055	2.65E-38	1.862	3.48E-12	Rittner and Bertrams[4]
202712_s_at	CKMT1A/ CKMT1B	Creatine kinase, mitochondrial 1A/creatine kinase, mitochondrial 1B	Arginine and proline metabolism	1.200	1.57E-06	1.556	1.14E-35	1.213	1.04E-11	Schlattner et al[5]
202870_s_at	CDC20	Cell-division cycle protein 20	Cell cycle, oocyte meiosis, ubiquitin-mediated proteolysis	1.345	2.61E-09	1.767	3.31E-39	1.251	2.58E-07	Gudjonsson et al[6] Mee et al[7]
203127_s_at	SPTLC2	Serine palmitoyltransferase, long chain base subunit 2	Sphingolipid metabolism	1.432	2.45E-12	1.629	0	1.807	1.53E-20	Yao et al[21]
216202_s_at	SPTLC2	Serine palmitoyltransferase, long chain base subunit 2	Sphingolipid metabolism	2.024	1.89E-11	2.095	0	2.106	2.43E-14	Yao et al[21]
203418_at	CCNA2	Cyclin-A2	Cell cycle, progesterone-mediated oocyte maturation	1.132	2.88E-08	1.797	5.75E-41	1.434	9.24E-10	Gudjonsson et al[6]
204385_at	KYNU	Kynureninase	Tryptophan metabolism	1.021	3.29E-09	2.455	0	1.859	1.65E-15	Gudjonsson et al[6]
210663_s_at	KYNU	Kynureninase	Tryptophan metabolism	2.133	2.15E-10	3.213	0	2.788	2.59E-16	Gudjonsson et al[6]
217388_s_at	KYNU	Kynureninase	Tryptophan metabolism	3.797	5.90E-13	1.497	4.61E-33	4.628	4.37E-22	Gudjonsson et al[6]
204751_x_at	DSC2	Desmocollin-2	Arrhythmogenic right ventricular cardiomyopathy	2.461	2.05E-06	2.573	2.26E-35	1.692	1.64E-08	Koczan et al[8]

(*Continued*)

Table S1 (*Continued*)

Probe ID	Gene Symbol	Gene title	Functional annotation on human Kegg pathways	GSE6710 Lesional versus nonlesional		GSE13355 Lesional versus nonlesional		GSE14905 Lesional versus nonlesional		Reference
				Log_2 fold change	Corrected *P*-value	Log_2 fold change	Corrected *P*-value	Log_2 fold change	Corrected *P*-value	
205476_at	CCL20	C-C motif ligand 20	Cytokine-cytokine receptor interaction, chemokine signaling pathway	1.932	7.39E-07	2.889	2.99E-35	2.664	4.69E-15	Suárez-Fariñas and Magnasco[22]
205990_s_at	Wnt5a		Wnt signaling pathway, hedgehog signaling pathway, melanogenesis, pathways in cancer, basal cell carcinoma	1.826	1.83E-09	2.335	3.20E-36	2.057	2.39E-17	Romanowska et al[9]
206166_s_at	CLCA2	Chloride channel, calcium activated, family member 2	Olfactory transduction	1.54	2.47E-05	1.369	2.44E-40	1.082	4.78E-10	Bowcock et al[23]
206561_s_at	AKR1B10	Aldo-keto reductase family 1 member B10	Fructose and mannose metabolism, linoleic acid metabolism, butanoate metabolism	4.163	4.69E-11	5.344	0	4.281	5.33E-24	Zhou et al[24]
207367_at	ATP12A	ATPase, H^+/K^+ transporting, nongastric, alpha polypeptide	Oxidative phosphorylation	2.264	6.41E-08	3.005	3.87E-37	3.271	2.43E-16	Nelson et al[10]
207387_s_at	GK	Glycerol kinase	Glycerolipid metabolism, PPAR signaling pathway	1.08	2.27E-06	1.958	5.57E-31	1.803	1.25E-13	Yao et al[21]
215977_x_at	GK	Glycerol kinase	Glycerolipid metabolism, PPAR signaling pathway	1.319	6.80E-06	1.655	5.74E-33	1.489	2.39E-11	Yao et al[21]
217167_x_at	GK	Glycerol kinase	Glycerolipid metabolism, PPAR signaling pathway	1.019	8.94E-06	1.220	3.45E-27	1.147	2.09E-12	Yao et al[21]
207463_x_at	PRSS3	Protease, serine 3	Neuroactive ligand-receptor interaction	1.398	3.03E-09	1.385	3.32E-31	1.418	7.68E-11	Lee et al[11]
213421_x_at	PRSS3	Protease, serine 3	Neuroactive ligand-receptor interaction	1.372	4.07E-09	1.368	2.41E-30	1.374	5.42E-11	Lee et al[11]
208650_s_at	CD24	Cluster of differentiation 24		2.611	9.65E-10	2.230	0	2.734	1.38E-19	Romanowska et al[2]
210164_at	GZMB	Granzyme B	Natural killer cell-mediated cytotoxicity, type 1 diabetes mellitus, autoimmune thyroid disease, allograft rejection, graft-versus-host disease	1.060	9.61E-06	2.961	4.05E-34	2.286	3.75E-14	Haider et al[27]
211075_s_at	CD47	Cluster of differentiation 47	Extracellular matrix receptor interaction	1.420	7.45E-09	1.642	0	1.910	3.15E-21	Romanowska et al[2]
213857_s_at	CD47	Cluster of differentiation 47	Extracellular matrix receptor interaction	1.252	3.22E-08	1.171	0	1.455	2.92E-20	Romanowska et al[2]
219403_s_at	HPSE	Heparanase	Glycosaminoglycan degradation	3.007	1.01E-13	3.753	0	3.542	1.72E-23	Yao et al[21]
214710_s_at	CCNB1	G2/mitotic-specific cyclin-B1	Cell cycle, oocyte meiosis, p53 signaling pathway, progesterone-mediated oocyte maturation	1.667	2.13E-09	2.479	6.80E-41	1.957	4.54E-12	Haider et al[12]

208992_s_at	STAT3	Signal transducer and activator of transcription 3	Chemokine signaling pathway, JAK-STAT signaling pathway, adipocytokine signaling pathway, pathways in cancer, pancreatic cancer, acute myeloid leukemia	1.469	4.07E-07	1.132	1.02E-28	1.247	1.04E-13	Irizarry et al[25]
210608_s_at	FUT2	Galactoside 2-alpha-L-fucosyltransferase 2	Glycosphingolipid biosynthesis, glycosphingolipid biosynthesis	1.042	6.69E-07	1.720	5.17E-24	1.437	2.84E-11	Ding et al[13]
219209_at	IFIH1	Interferon-induced helicase C domain-containing protein 1	RIG-I-like receptor signaling pathway	1.156	0.003	1.387	3.46E-23	1.530	7.60E-12	Li et al[14]
202687_s_at	TNFSF10	Tumor necrosis factor (ligand) superfamily, member 10	Cytokine-cytokine receptor interaction, apoptosis, natural killer cell-mediated cytotoxicity	1.011	0	1.105	2.02E-24	1.217	3.11E-12	Shannon et al[26]
206177_s_at	ARG1	Arginase 1	Arginine and proline metabolism	1.592	1.50E-06	1.411	1.06E-20	1.897	7.77E-12	Bruch-Gerharz et al[15]
203180_at	ALDH1A3	Aldehyde dehydrogenase 1 family, member A3	Glycolysis/gluconeogenesis, histidine metabolism, tyrosine metabolism, phenylalanine metabolism, metabolism of xenobiotics by cytochrome P450, drug metabolism	1.142	7.53E-05	1.639	1.16E-20	1.953	7.37E-11	Romanowska et al[2]
201860_s_at	PLAT	Plasminogen activator, tissue	Complement and coagulation cascades	1.721	2.80E-06	2.012	2.19E-19	1.482	7.96E-06	Romanowska et al[2]
210904_s_at	IL13RA1	Interleukin 13 receptor, alpha 1	Cytokine-cytokine receptor interaction, JAK-STAT signaling pathway	1.202	4.11E-05	1.325	2.31E-20	1.474	2.08E-09	Wongpiyabovorna et al[16]
211612_s_at	IL13RA1	Interleukin 13 receptor, alpha 1	Cytokine-cytokine receptor interaction, JAK-STAT signaling pathway	1.012	0	1.168	1.87E-17	1.428	4.73E-11	Wongpiyabovorna et al[16]
213562_s_at	SQLE	Squalene epoxidase	Steroid biosynthesis	1.177	0	1.228	5.03E-16	1.679	3.73E-08	Oestreicher et al[28]
203665_at	HMOX1	Heme oxygenase 1	Porphyrin and chlorophyll metabolism	1.138	1.31E-09	1.076	1.13E-12	1.179	3.89E-09	Haider et al[12]
204941_s_at	ALDH3B2	Aldehyde dehydrogenase family 3 member B2	Glycolysis/gluconeogenesis, histidine metabolism, tyrosine metabolism, phenylalanine metabolism, metabolism of xenobiotics by cytochrome P450, drug metabolism	1.742	9.80E-07	1.308	1.22E-07	1.555	1.39E-05	Taylor et al[17]
205157_s_at	KRT17	Keratin 17		1.620	1.29E-05	1.654	4.71E-20	2.065	8.52E-10	Gudmundsdottir et al[18]
212236_x_at	KRT17	Keratin 17		1.048	0.002	1.125	1.26E-19	1.517	8.50E-10	Gudmundsdottir et al[18]
214580_x_at	KRT6/ KRT6/ KRT6C	Keratin 6A/keratin 6B/ keratin 6C		1.956	4.10E-07	2.383	5.42E-37	2.790	3.02E-18	Mommers et al[19]
216470_x_at	PRSS1	Trypsin 1	Neuroactive ligand-receptor interaction	1.200	3.89E-09	1.228	1.79E-29	1.298	1.51E-12	Iwakiri et al[20]

Note: References cited are given in the Supplementary reference list.

Table S2 Probe sets for genes found to be significantly upregulated in lesional versus nonlesional skin samples from each of the three experiments, ie, GSE6710, GSE13355, and GSE14905, and have not been previously linked to the pathogenesis of psoriasis

Probe ID	Gene Symbol	Gene title	Functional annotation on human Kegg pathways	GSE6710 Lesional versus nonlesional		GSE13355 Lesional versus nonlesional		GSE14905 Lesional versus nonlesional	
				Log_2 fold change	Corrected *P*-value	Log_2 fold change	Corrected *P*-value	Log_2 fold change	Corrected *P*-value
201890_at	RRM2	Ribonucleotide reductase subunit M2	Purine metabolism, pyrimidine metabolism, glutathione metabolism, p53 signaling pathway	1.869	4.38E-09	2.191	3.47E-35	1.874	7.05E-11
209773_s_at	RRM2	Ribonucleotide reductase subunit M2	Purine metabolism, pyrimidine metabolism, glutathione metabolism, p53 signaling pathway	1.989	4.77E-09	3.116	0	2.257	1.34E-12
203234_at	UPP1	Uridine phosphorylase 1	Pyrimidine metabolism, drug metabolism	1.669	8.22E-10	2.309	1.31E-36	2.159	1.82E-14
203256_at	CDH3	Cadherin-3	Cell adhesion molecules	1.308	9.61E-06	1.724	8.23E-34	1.124	2.93E-08
203560_at	GGH	Gamma-glutamyl hydrolase	Folate biosynthesis	1.478	4.20E-06	1.554	9.43E-33	1.693	1.33E-13
205349_at	GNA15	Guanine nucleotide-binding protein subunit alpha-12	Calcium signaling pathway	1.225	4.19E-08	1.232	4.23E-29	1.344	1.18E-16
205595_at	DSG3	Desmoglein-3		1.839	3.02E-06	1.625	3.38E-37	1.075	7.33E-10
210559_s_at	CDC2 or Cdk1	Cyclin dependent kinase 1	Cell cycle, oocyte meiosis, p53 signaling pathway, gap junction, progesterone-mediated oocyte maturation	1.182	1.17E-06	1.798	8.36E-34	1.261	2.42E-08
208651_x_at	CD24	Cluster of differentiation 24		1.511	2.81E-09	1.601	4.08E-41	2.238	1.15E-17
209771_x_at	CD24	Cluster of differentiation 24		1.297	1.67E-09	1.354	5.30E-42	2.026	1.29E-16
209772_s_at	CD24	Cluster of differentiation 24		2.296	7.42E-11	2.364	0	2.701	1.10E-16
216379_x_at	CD24	Cluster of differentiation 24		1.418	2.16E-09	1.482	9.80E-43	2.147	1.10E-16
266_s_at	CD24	Cluster of differentiation 24		1.672	4.67E-12	1.714	1.81E-39	2.239	1.48E-17
209125_at	KRT6A	Keratin 6A		1.732	4.79E-05	2.489	3.11E-37	2.770	3.27E-17
209126_x_at	KRT6B	Keratin 6B		1.369	0	2.076	2.28E-38	2.100	1.25E-11
209800_at	KRT16	Keratin 16		3.877	7.17E-08	4.121	0	3.846	1.41E-17
214581_x_at	TNFRSF21	Tumor necrosis factor receptor superfamily, member 21	Cytokine-cytokine receptor interaction	1.202	0	1.476	4.81E-27	1.613	1.44E-11
202934_at	HK2	Hexokinase 2	Glycolysis/gluconeogenesis, fructose and mannose metabolism, galactose metabolism, starch and sucrose metabolism, amino sugar and nucleotide sugar metabolism, insulin signaling pathway, type 2 diabetes mellitus	1.066	6.69E-06	1.398	2.26E-32	1.191	1.73E-13
210087_s_at	MPZL1	Myelin protein zero-like protein 1	Cell adhesion molecules	1.111	1.24E-06	1.222	6.48E-30	1.144	1.73E-09
215966_x_at	GK3P	Glycerol kinase 3 pseudogene	Glycerolipid metabolism, PPAR signaling pathway	1.190	7.18E-07	1.328	8.37E-26	1.197	7.70E-11
207381_at	ALOX12B	Arachidonate 12-lipoxygenase, 12R type	Arachidonic acid metabolism	1.805	2.40E-11	1.785	9.47E-25	1.689	1.63E-13

206643_at	HAL	Histidine ammonia-lyase	Histidine metabolism, nitrogen metabolism	1.434	1.93E-05	1.635	1.65E-19	2.308	1.95E-15
209924_at	CCL18	Chemokine (C-C motif) ligand 18	Cytokine-cytokine receptor interaction, chemokine signaling pathway	1.152	0.004	2.737	5.74E-23	2.050	1.48E-04
32128_at	CCL18	Chemokine (C-C motif) ligand 18	Cytokine-cytokine receptor interaction, chemokine signaling pathway	1.480	0.001	2.611	2.98E-22	1.896	1.68E-05
210020_x_at	CALML3	Calmodulin-like protein 3	Calcium signaling pathway, phosphatidylinositol signaling system, oocyte meiosis, vascular smooth muscle contraction, long-term potentiation, neurotrophin signaling pathway, olfactory transduction, insulin signaling pathway, gonadotropin-releasing hormone signaling pathway, melanogenesis, Alzheimer's disease, glioma	1.326	4.01E-06	1.381	8.91E-20	1.267	6.45E-08
215465_at	ABCA12	ATP-binding cassette sub-family A member 12	ABC transporters	1.596	4.12E-09	1.503	7.34E-27	1.728	1.61E-14

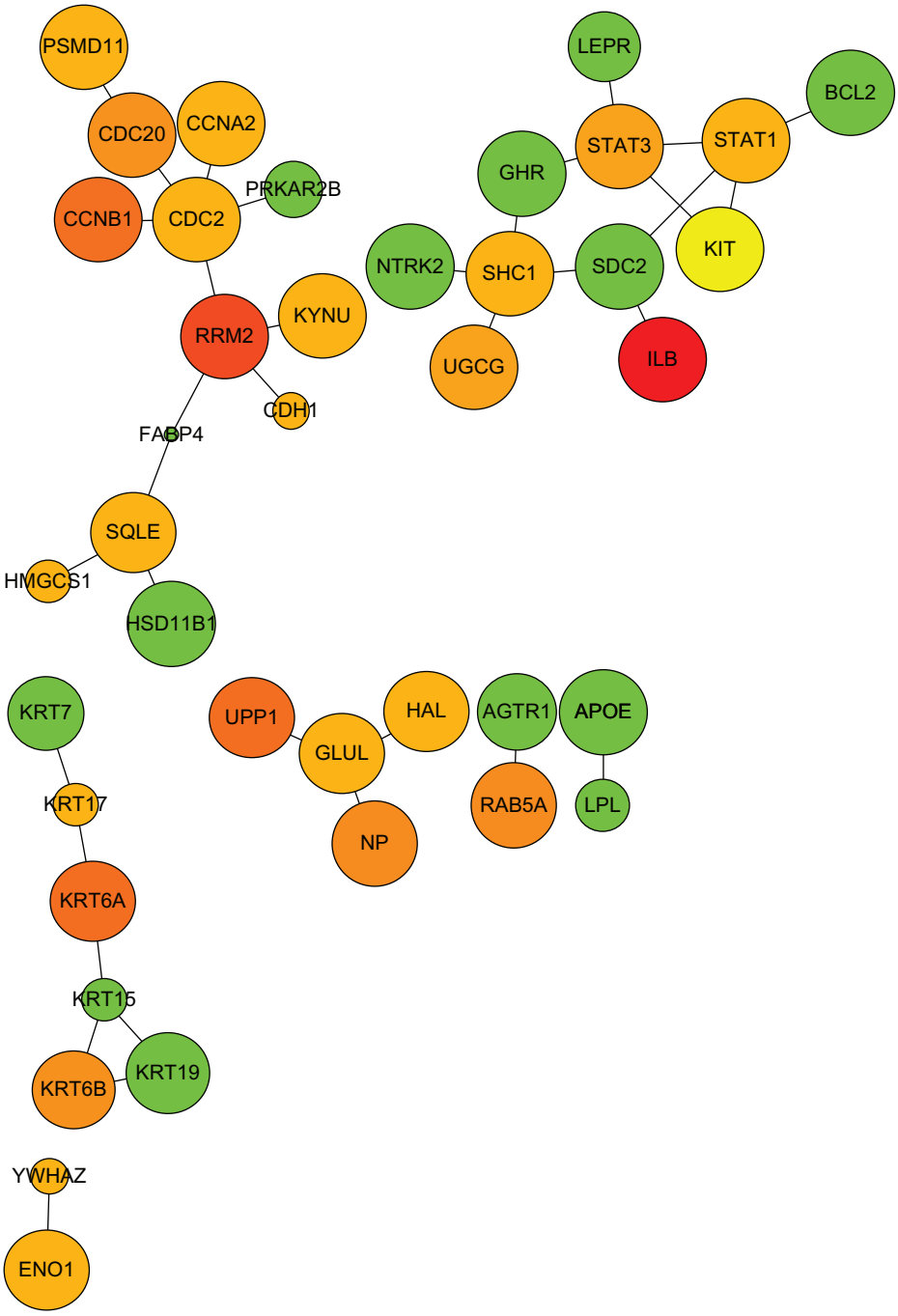

Figure S1 Network analysis (netAnalyse.py method, setting shortest path threshold =1 and *P*-value threshold =0.05) shows possible interaction between the potential gene targets for treatment of psoriasis as identified in this study from the GSE6710 experiment.[29] The network was edited in Cytoskape, with a force-directed layout applied. Green circles indicate downregulated genes, yellow-orange-red circles indicate upregulated genes, with red showing strongest and yellow showing least upregulation. Size of the nodes indicates the level of significance, with larger nodes showing a lower FDR (higher significance). Lines connecting nodes show direct interactions between genes.

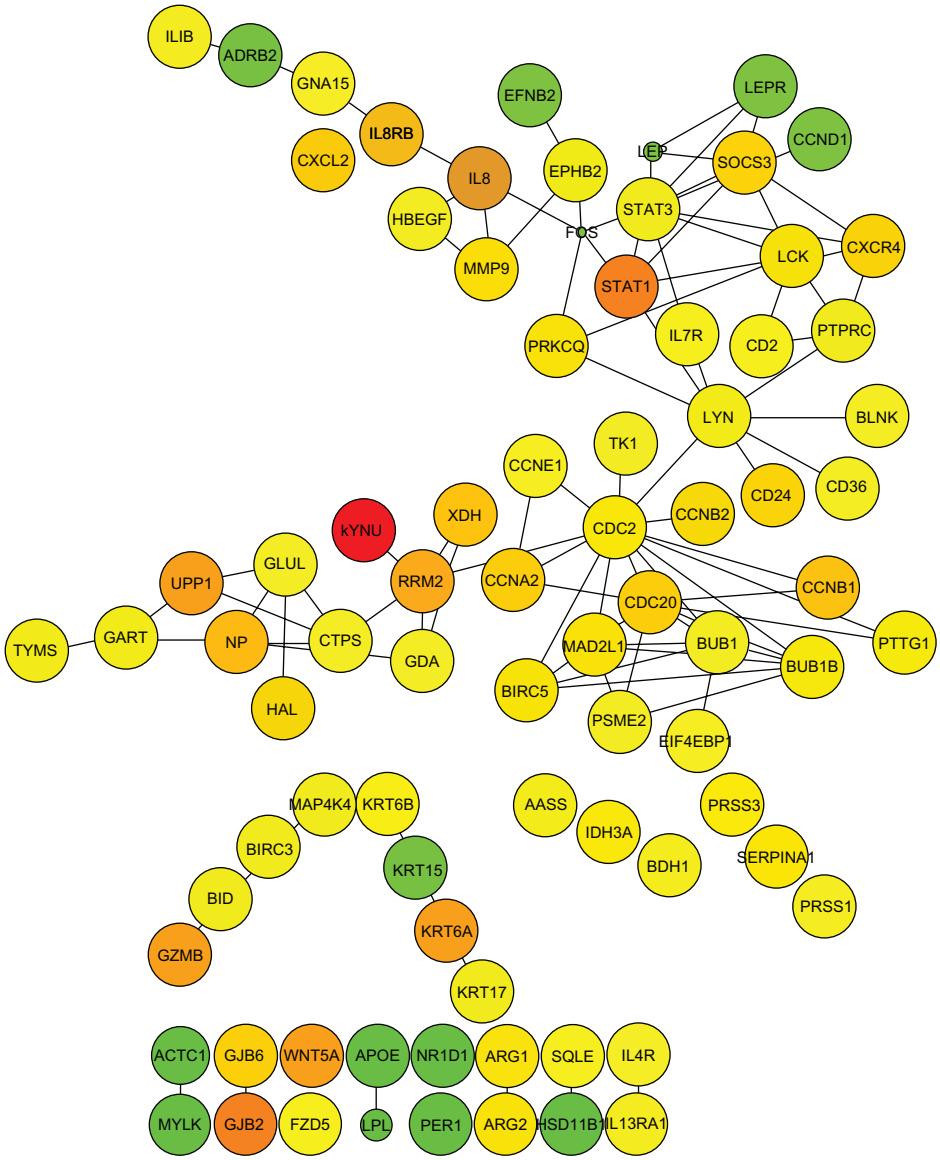

Figure S2 Network analysis (netAnalyse.py method, setting shortest path threshold =1 and *P*-value threshold =0.05) shows possible interaction between potential gene targets for the treatment of psoriasis as identified in this study from the GSE13355 experiment.[30] The network was edited in Cytoskape, with a force-directed layout applied. Green circles indicate downregulated genes, yellow-orange-red circles indicate upregulated genes, with red showing strongest and yellow showing least upregulation. Size of the nodes indicates the level of significance, with larger nodes showing a lower FDR (higher significance). Lines connecting nodes show direct interactions between genes.

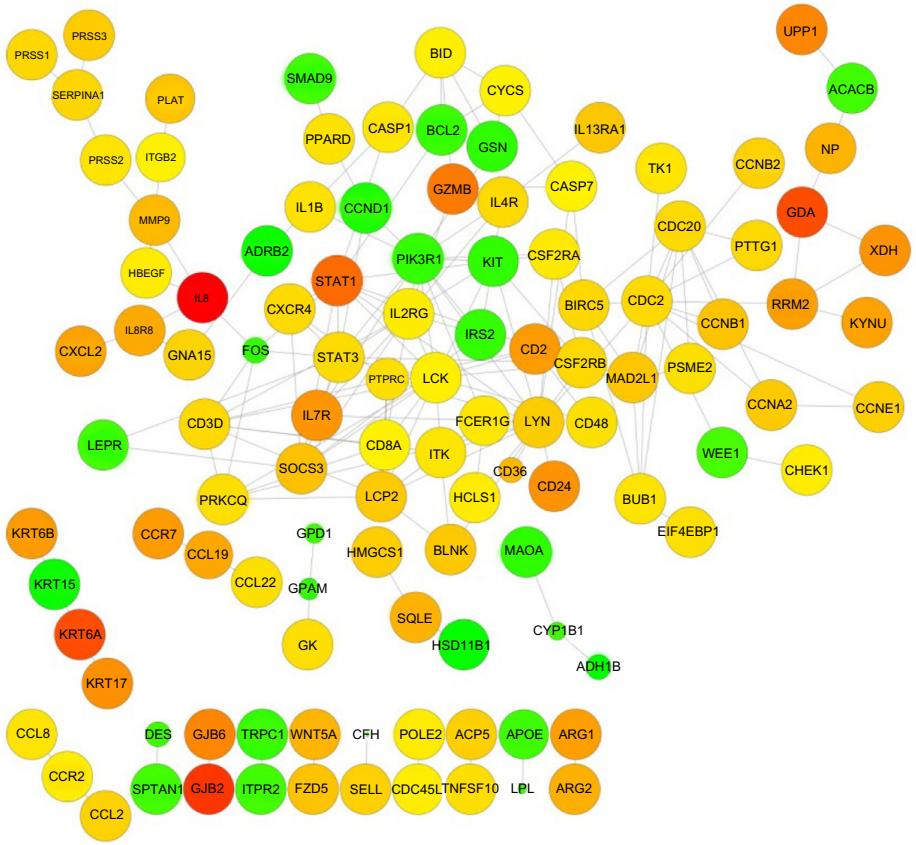

Figure S3 Network analysis shows possible interaction between the potential gene targets for the treatment of psoriasis as identified in this study from the GSE14905 experiment[21] (green circles indicate downregulated genes and orange/red circles indicate upregulated genes).

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