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REVIEW

Looking within the lesion: Large scale transcriptional profiling of psoriatic plaques

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Abstract

Psoriasis is a lifelong, chronic, recurring and highly variable skin disease. Psoriatic plaques are formed through induction of inflammation in the epidermis and deregulation of keratinocyte proliferation and differentiation. This results in red or silvery scaly patches on the surface of the epidermis. To look within the lesions and define the changes in gene expression in psoriasis, investigators compared the transcriptomes of psoriatic plaques, of uninvolved skin of patients and of skin from healthy individuals. In several large studies with many patients, the genes expressed at much higher level in psoriatic plaques included those responsible for the cell cycle, keratinocyte differentiation, and response to wounding; conversely, lipid and fatty acid metabolism enzymes were expressed at reduced levels. The nonlesional and healthy skin appeared fairly similar. The largest study included paired biopsies from 85 individual patients. The same group used transcription profiling to follow the course of treatment in a set of patients, and correlated changes in the transcriptome of blood samples of psoriatic patients. Importantly, a noninvasive technique involving tape-stripping of skin, has been shown effective in transcriptional studies of psoriasis. Current efforts are focused on deconvoluting the contributions of various cell types in psoriasis, keratinocytes, lymphocytes, fibroblasts etc. Taken as a whole, these efforts will lead to personalized medicine, *i.e.*, to specific, individualized treatments of patients with psoriasis.

Key words: Cytokines; Inflammation; Metaa nalysis; Microarrays; Skinomics

Core tip: Dermatology was among the first medical specialties to adopt bioinformatics methodology, and Psoriasis, with its high prevalence, among the first diseases. Genome-wide association studies identified close to 50 genetic predisposition loci, to date. Recently, large-scale transcriptome analysis using DNA microarrays identified the important signaling pathways and regulators of gene expression in psoriasis. These efforts, and the fundamental knowledge they provide will lead to personalized medicine, *i.e.*, to specific, individualized treatments of psoriatic patients in the near future.

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INTRODUCTION

According to the National Psoriasis Foundation, psoriasis affects 7.5 million Americans and 125 million people worldwide. It is a chronic autoimmune disease with a multifactorial (genetic and environmental) etiology[1].

Table 1 Psoriasis susceptibility loci identified using genome-wide association studies

Psoriasis	Chromosome	Gene	Locus	Ref.
1	1p31.3	*IL-23R*		Nair *et al*[11]
1	1p31.3	*IL-23R*		Liu *et al*[48]
1	1p31.3	*IL-23R*	rs9988642	Tsoi *et al*[8]
2	1p36	*RUNX3*	rs7536201	Tsoi *et al*[8]
3	1p36.11	*IL28RA*	rs7552167	Tsoi *et al*[8]
4	1p36.23	*SLC45A1, TNFRSF9*	rs11121129	Tsoi *et al*[8]
5	1q21	*PSORS4*		Julià *et al*[49]
6	1q21	*LCE3D*	rs6701216	Liu *et al*[48]
7	1q21.3	*LCE3B*	rs4112788	de Cid *et al*[1]
8	20q12-q13.12	*NCOA5*	rs2903908	Zervou *et al*[50]
9	20q12-q13.2	*CD40*	rs4810485	Zervou *et al*[50]
10	20q13.13	*RNF114*	rs1056198	Tsoi *et al*[8]
11	22q11.21	*UBE2L3*	rs4821124	Tsoi *et al*[8]
12	2p15	*B3GNT2*	rs10865331	Tsoi *et al*[8]
13	2p16.1	*FLJ16341, REL*	rs62149416	Tsoi *et al*[8]
14	2q14.2	*IL1RN*		Julià *et al*[49]
15	2q24.2	*KCNH7, IFIH1*	rs17716942	Tsoi *et al*[8]
16	3p12.1	*CADM2*		Hiruma *et al*[51]
17	4q27			Liu *et al*[48]
18	5q15	*ERAP1*	rs27432	Tsoi *et al*[8]
19	5q31	*IL-13, IL-4*	rs1295685	Tsoi *et al*[8]
20	5q31.1-q33.1	*IL-12B*	rs12188300	Tsoi *et al*[8]
21	5q32-q33.1	*TNIP1*	rs17728338	Bowes *et al*[52]
22	6p21.3	*HLA-C*		Knight *et al*[53]
23	6p25.3	*EXOC2, IRF4*	rs9504361	Tsoi *et al*[8]
24	6q21	*TRAF3IP2*	rs33980500	Ellinghaus *et al*[10]
25	6q23	*TNFAIP3*	rs582757	Tsoi *et al*[8]
26	6q25.3	*TAGAP*	rs2451258	Tsoi *et al*[8]
27	7p14.1	*ELMO1*	rs2700987	Tsoi *et al*[8]
28	9p12	*DDX58*	rs11795343	Tsoi *et al*[8]
29	9q31	*KLF4*	rs10979182	Tsoi *et al*[8]
30	9q34	*TSC1*	rs1076160	Bowes *et al*[52]
31	10q22.3	*ZMIZ1*	rs1250546	Tsoi *et al*[8]
32	11q11-q13	*RPS6KA4, PRDX5*	rs645078	Tsoi *et al*[8]
33	11q22.3	*ZC3H12C*	rs4561177	Tsoi *et al*[8]
34	11q23.3	*ETS1*	rs3802826	Tsoi *et al*[8]
35	12q13.3	*STAT2, IL23A*	rs2066819	Tsoi *et al*[8]
36	13q12	*LHFP*		Liu *et al*[48]
37	13q14.11	*COG6*	rs7993214	Liu *et al*[48]
38	14q13	*NFKBIA*	rs8016947	Tsoi *et al*[8]
39	15q21		rs3803369	Liu *et al*[48]
40	16p11.2	*PRSS53, FBXL19*	rs12445568	Tsoi *et al*[8]
41	16p13.13	*PRM3, SOCS1*	rs367569	Tsoi *et al*[8]
42	17q11.2-q12	*NOS2*	rs28998802	Tsoi *et al*[8]
43	17q21.31	*PTRF, STAT3, STAT5A/B*	rs963986	Tsoi *et al*[8]
44	17q25	*CARD14*	rs11652075	Tsoi *et al*[8]
45	18q21.2	*POL1, STARD6, MBD2*	rs545979	Tsoi *et al*[8]
46	18q22.1	*SERPINB8*		Julià *et al*[49]
47	19p13.2	*TYK2*	rs34536443	Tsoi *et al*[8]
48	19p13.2	*ILF3, CARM1*	rs892085	Tsoi *et al*[8]

Note that many of the loci were identified in multiple studies (*e.g.*, shaded).

Past research suggests that external, internal and/or environmental triggers, such as stress, systemic illnesses and environmental allergens, combined with the genetic predisposition, may result in an altered immunity and an increased risk for the development of psoriasis[2]. However, the initial trigger for psoriasis and development of psoriatic lesions remains unknown[3-5]. While the exact causes are unknown, in psoriasis the immune system sends out incorrect signals that speed up the proliferation of epidermal keratinocytes. While normal keratinocytes mature and desquamate in about a month, psoriatic skin ones reach the surface in only 3-4 d and, instead of sloughing off individually, they accumulate to form large flaking scraps of skin[2].

Psoriasis is typically a lifelong, chronic recurring condition. It can vary in severity from small localized areas to covering the entire body. The diagnosis of psoriasis is based on the appearance of skin, not on blood tests or specialized diagnostic procedures. Occasionally a skin biopsy may be needed to rule out other proliferative skin disorders. Psoriatic plaques are formed through an increase in inflammation in the epidermis, deregulation of cell cycle processes, increase in keratinocyte proliferation and epidermal differentiation changes. Together this results in the formation of raised, red or silvery scaly patches on the surface of the stratum corneum.

The genetic predisposition for psoriasis was known through family-based and population-based epidemiological studies, which suggested that genetic factors play a key role in the development of psoriasis[6-7]. Perhaps a third of psoriatic patients report a family history of psoriasis; reports on monozygotic twins find a 70% chance of a twin developing psoriasis if the other twin has psoriasis while this number is around 20% for paternal twins. More recently, genome-wide association scans have fine-mapped the nine susceptibility loci (PSORS1-PSORS9) and located many previously unsuspected genomic markers on human chromosomes[6,8-11]. A current list of psoriasis susceptibility loci is given in Table 1. However, the known genetic factors for psoriasis do not account for all observed genetic susceptibility to psoriasis; additional genetic factors remain to be discovered[6]. Thus, the genetic contribution to psoriasis is not fully understood[3].

Of the five types of psoriasis (plaque, guttate, inverse, pustular, and erythrodermic), the most common is the plaque psoriasis. Plaque psoriasis is seen as red and white silvery hues of scaly patches appearing on the top of the epidermis. Plaques frequently occur on the extensor aspects of the knees and elbows, but can affect any area, including the scalp, genitals, palms and soles. Fingernails and toenails are often affected, which can be an independent symptom. Additionally, psoriasis can be associated with inflammation of the joints, which is known as psoriatic arthritis. Guttate psoriasis presents as numerous small, scaly, pink or red lesions over large areas of the body, the trunk, limbs and scalp. Inverse or flexural psoriasis occurs in skin folds, *e.g.*, around the genitals, the armpits or under the breasts. Pustular psoriasis presents as raised pus-filled bumps, commonly on the hands and feet (*i.e.*, palmoplantar pustulosis), or generalized, occurring randomly widespread on any part of the body. Erythrodermic psoriasis involves the widespread inflammation

Table 2 Transcriptional profiling studies targeting psoriasis in the GEO database

	Microarrays	Platform	Samples	Ref.
Comparison studies				
GSE34248	14 + 14	HG-U133_Plus_2	Lesional + NonLes	[21]
GSE41662	24 + 24	HG-U133_Plus_2	Lesional + NonLes	[21]
GSE41663	15 + 15 (+ 51 treated)	HG-U133_Plus_2	Lesional + NonLes	[21]
GSE30999	85 + 85	HG-U133_Plus_2	Lesional + NonLes	[19]
GSE11903	15 + 15 (+ 59 treated)	HG-U133A_2	Lesional + NonLes	[18]
GSE6710	13 + 13	HG-U133A	Lesional + NonLes	[24]
GSE14905	21 + 33 + 30	HG-U133_Plus_2	Healthy + Les + NonLes	[16]
GSE13355	64 + 58 + 58	HG-U133_Plus_2	Healthy + Les + NonLes	[12]
GSE32407	20 + 20 (+ 20 IFNg treated)	HG-U133A_2	Healthy + NonLes	[17]
Related studies				
GSE42305			Monocytes	[54]
GSE41905			Kcytes transfected wt Antimir31	[55]
GSE31652			All lesional, treated placebo	[56]
GSE26952			Nonlesional only Psor AD	[57]
GSE18948			PBMCs	[58]
GSE11307			PCR study	[1]
GSE6601			Psor *vs* AD	[59]
GSE41745	3 + 3		RNA Sequencing	[60]
GSE26866	11 + 11 (different regions)	HG-U133A_2	Single *vs* double amplification	[61]
GSE30768	2 +4 (+ 8 flare and relapse)	HG-U133A_2	Small number of samples	[62]
GSE2737	3 + 4 + 4	HG_U95Av2	Small array	[63]

[1]Shin J and Detmar M, unpublished. PBMCs: Peripheral blood mononuclear cell; PCR: Partido comunista revolucionario.

and exfoliation over most of the body skin. While the shared symptoms, *i.e.*, the underlying inflammation and epidermal hyperproliferation, characterize all types of psoriasis, the distinct clinical presentations, the extensive and dispersed genetic underpinnings and inconsistent, variable clinical responses argue that psoriasis comprises a cluster of related but distinct disorders.

The superb international success in GWAS mapping the psoriasis susceptibility loci has been joined recently by equally outstanding transcriptional profiling studies from several laboratories that recruited very impressive numbers of patients and samples (Table 2). These studies provide deep and comprehensive insights into the molecular mechanisms of the pathology of psoriasis. Also an international effort, the transcriptional profiling is lead by two teams in the United States, that of Drs. G. Gudjonsson and J.T. Elder at the University of Michigan, and the team of Dr. J.G. Krueger at the Rockefeller University. The researchers compared the genes expressed in psoriatic plaques with those expressed in the nonlesional skin of patients, and both of these with the skin of healthy control subjects. Investigators also searched for diagnostic markers of psoriasis in the blood of patients. The current status and insights from these efforts is the subject of this review.

DISCUSSION

In a very influential study Gudjonsson *et al*[12] analyzed a large cohort of psoriatic patients and healthy controls using transcriptional profiling. Importantly, their analysis included 58 paired samples of lesional and nonlesional skin, allowing comparisons of matched samples from the same patients, and 64 control biopsies, allowing large-scale comparisons of lesional and nonlesional skin with healthy skin[11-15]. The sheer size of this study allowed the authors to identify close to a thousand differentially expressed genes in the lesional skin. The genes over-represented in the psoriasis lesions included Serpins, β-defensin-2, *S100A* genes and IL-8. Suppressed genes included β-cellulin, *IL1F7* and *CCL27*. The ontological categories induced in the lesions incorporated cell cycle, expected in this hyperproliferative disease, keratinocyte differentiation markers and three categories that contained cytokines, chemokines and their receptors, namely immune response, defense response and response to wounding[14]. The suppressed ontological categories incorporated lipid and fatty acid metabolism. The nonlesional and healthy skin, however, appeared rather similar, confirming the results of Yao *et al*[16] (see below).

In an important follow-up a team in United Kingdom, collaborating with Dr Gudjonsson, used sophisticated bioinformatics methodologies to classify psoriatic patients and identify distinct molecular subtypes[15]. Again, the nonlesional and healthy skin appeared quite similar. Among the psoriatic plaque samples, two subtypes were identified using multidimensional scaling, one a tightly clustered group of patients at the apex of the less congruent and more dispersed subtype. The authors proposed that TGF and the ErbB pathways may be involved in distinguishing the two subtypes.

The ground-breaking large-scale transcriptional profiling of psoriatic samples was reported by the team of Dr Krueger in 2009[16]. They analyzed 33 lesional, 30 nonlesional and 21 healthy control samples. The nonlesional skin was more similar to healthy skin of other donors that to the lesional skins from the same patient. The transcriptional signatures of the plaque biopsies pointed to the infiltration of T cells and dendritic cells in the lesions. Yao *et al*[16] recognized the signatures of several cytokines implicated in psoriasis. Specifically, they compared genes differentially expressed in the lesions with the gene sets regulated by IFN-α, IFN-γ and by TNF-α in keratinocytes. The significant overlaps substantiated the proposed roles of these cytokines in psoriasis. Several members of IFN-α family, IFN-α1, IFN-α2, IFN-α6, IFN-α7, IFN-α8, IFN-α14 and IFN-α21, were overexpressed in the lesions. The results validated the TNF-α-targeting and the T cell targeting therapies currently in wide use to

treat psoriasis, as well as suggested IFN-α as a potential target.

Interestingly, in a separate study, Dr. Krueger's team found that a single injection of IFN-γ into the dermis of nonlesional sites of psoriatics can recapitulate the transcription profile changes seen in the psoriatics plaques[17]. Apparently, IFN-γ can initiate the psoriasiform immune responses by promoting influx of T cells and dendritic cells. A similar influx was seen even in the IFN-γ-injected sites of healthy, non-psoriatic individuals.

The same team followed transcriptional changes in psoriatic patients treated with Etanercept[18]. Baseline transcriptional profiles were compared with those in treatment for up to 12 wk. The patients were divided into responders (11 patients) and non-responders (4 patients). Interestingly, the TNF-α-regulated genes (*e.g., IL-1β* and *IL-8*) were silenced in both groups; however the responders specifically inactivated the genes associated with the Th17 immune responses. The study highlighted the distinguishing and important role of the Th17 pathway in the pathology of psoriasis.

The largest transcriptional profiling study of psoriasis patients, to date, was reported by Suárez-Fariñas *et al*[19] in 2012. The Rockefeller University team compared 85 matched pairs of lesional and nonlesional biopsies from patients. The impressively large study identified 2725 individual genes differentially expressed 2-fold or more in the plaques. Serpins and S100A proteins were among the most overexpressed genes, but also many proteases/peptidases, including Kallikrein-related peptidase-6, -13, *etc*. Conversely, β-cellulin, CCL27 and lipid and fatty acid metabolism enzymes were found suppressed in the plaques, as seen by others[12,19]. The authors confirmed the results of transcriptional profiling using extensive RT-PCR and immunohistological experiments.

In this study by Suárez-Fariñas *et al*[19], the sets of regulated genes were compared with the sets identified in two previous studies[12,16]. Very high correlation was seen (scores ranging from 0.83 to 0.94) demonstrating very high concordance of the gene expression changes in psoriasis across the three large studies in two different centers. The concordance among different studies received extensive scrutiny[20-21], and it was found that, provided appropriate statistical methodologies are used, the studies are very highly concordant. The concordance allowed a meta analysis of psoriasis transcriptomics studies[22]. The meta analysis identified over 1000 genes that were consistently differentially expressed over 5 different studies. Moreover, this study provided a link between changes in the psoriasis transcriptome and atherosclerosis signaling, lipid and fatty acid metabolism and cardiovascular disease, thus providing a crucial link between the psoriatic skin conditions and these systemic diseases. Tian *et al*[22] in 2012, defined a "core" 20-gene set that distinguishes the psoriatic lesions. Interestingly, this core contained genes overexpressed even in psoriatic skin after successful treatment, as well as distinct genes epigenetically labeled by differential methylation in plaques.

Suárez-Fariñas *et al*[19] also compared serum protein levels of 12 important secreted proteins detected as overrepresented in psoriatic plaques[19]. In large cohort of approximately 150 patients and as many controls, all 12 proteins were found at increased levels in the sera of patients. The proteins included CCL2, CCL22, CXCL5 and TNF-α, which are all markers of psoriasis.

Using transient unresponsiveness to the stimulation of dendritic cells as a model of chronic inflammation, such as in psoriasis, Filkor *et al*[23] found the expression of feedback regulators of innate immunity to be suppressed, such as TNFAIP3 and TNFAIP8; these are also suppressed in the dermis of psoriatic patients.

In a study of matched lesional and nonlesional samples from 13 patients, in 2007, Reischl et al. identified 179 genes differentially expressed 2-fold or more[24]. Interestingly, 16 statistically significant genes were associated with the Wnt/β-catenin pathway, leading the authors to propose an important role for this pathway in psoriasis. Attempts to distinguish differences in the transcriptomes of plaques from different body sites, and between patients with symmetric and asymmetric plaques have not been successful[25]. In a more limited study of just 44 genes, Aubert *et al*[26] found that in psoriasis of the scalp, treatment with topical steroids restores expression of the 10 inflammation-related genes to the more basal, healthy levels. Similar results were found in a study of 5 lesional and 5 nonlesional samples, compared with similar number of blood samples[27]. Using a completely different approach, involving meta analysis of data in public repositories, specifically the BodyMap gene expression database[28], and RNA sequencing, Itoh *et al*[29] found very similar sets of differentially expressed genes. Others have noted the overlaps between genes differentially expressed in psoriasis and regulated by cytokines in epidermal keratinocytes[30-36].

In a study of matched lesional and nonlesional samples from 15 patients and 6 healthy controls, the team of Bowcock *et al*[37] a collaboration of Washington U. and Baylor U., also found overexpression of serpins and S100A proteins, but also of keratins KRT6, KRT16 and KRT17, known markers of epidermal hyperproliferation[38]. These studies also addressed the transcription factors responsible for the expression of differentially expressed genes and found NF-κB and AP1 sites evident, as expected. In addition, sites for nuclear receptors, RORa1, VDR and PPAR are found in the regulated genes, as are the motifs bound by Ikaros proteins, zinc finger transcription factors characteristic for lymphoid cell lineages. A similar set of transcription factors associated with psoriasis, additionally including E2F1 was proposed in another study[39]. Using a completely different approach, involving proteomics, NF-κB, AP1, STAT1 and STAT3 proteins were identified as important in psoriasis transcriptional deregulation[40].

In an exciting and sophisticated skinomics approach, Swindell *et al*[41] were able to assign most of the differentially expressed genes in the psoriatic plaques to the

different cell types that contribute to the disease[41]. Specifically, they found that the genes induced in the plaques derive mainly from the activated keratinocytes, 56%, infiltrating T-cells, 14%, and macrophages, 11%. The suppressed genes were derived from the adipose, epidermis and dermis 4%. Swindell *et al*[41] also distinguished the patients who responded to Etanercept from the non-responders by their respective transcriptional profiles. Moreover, they confirmed the induction of genes responding to several cytokines, including IFN-γ, IL-1, IL-17A and TNF-α.

Importantly, skin samples can be obtained using noninvasive and (almost) painless technique of tape-stripping. This method provides RNA samples of quality and quantity adequate for microarray analysis[42]. Using tape-stripping followed by RT-PCR, Benson *et al*[43] have detected increased levels of mRNAs for TNFα, IFγ and KRT16, among others, in psoriatic plaques.

CONCLUSIONS AND FUTURE PROSPECTS

Whereas the future is inherently unpredictable, currently several trends seem to guide the research in transcriptional changes in psoriasis. First, stratification of patients into categories (*e.g.*, etanercept responders) will allow personalized medicine approaches to be developed and used in the treatment of psoriasis. Second, the exact roles of the immune cell types, the cytokines and chemokines they produce and the signaling pathways consequently activated in the responding keratinocytes will provide scores of additional targets, which will further advance patient-specific treatments. And third, an exciting new area of research, that of the effects of the cutaneous microbiome on psoriasis initiation, progression and resolution[44-47] has the potential to revolutionize our conceptual and practical approach to this intractable and difficult problem.

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