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Study on Certain Biomarkers of Inflammation in Psoriasis Through "OMICS" Platforms

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Abstract: *Background:* In recent years, research on psoriasis has focused on the identification of biomarkers for the diagnosis, pathogenesis, prognosis, or therapeutic response of the disease. These studies could provide insights into the susceptibility and natural history of psoriasis. The identification of biomarkers related to comorbidities in psoriasis, such as arthritis, cardiovascular disease, and the metabolic syndrome, is of special clinical interest.

Materials and Methods: We performed an extensive review on psoriasis biomarkers, including cytokine and growth factors, in the literature published between 1997 and 2013, including cross-references of any retrieved articles. We also included some data from our own studies.

Results: This review presents current knowledge of soluble biomarkers in psoriasis, including cytokines, chemokines, proangiogenic mediators, growth factors, antimicrobial proteins, neuropeptides, and oxidative stress markers.

Conclusion: In conclusion, a number of studies have been conducted with the aim of establishing soluble biomarkers for psoriasis. Most of the biomarkers that have been studied do not meet the criteria for a clinically useful biomarker. Further work is needed to establish a role for soluble biomarkers in the diagnosis and treatment of psoriasis, with a special focus on biomarkers for psoriasis comorbidities, such as arthritis, cardiovascular disease, and the metabolic syndrome.

Keywords: Biomarker, cytokine, growth factor, psoriasis.

1. INTRODUCTION

Psoriasis is a common skin disorder affecting about 3% of the world population. It is characterized by relapsing skin lesions displaying epidermal hyperplasia, an inflammatory infiltrate, and angiogenesis. The inflammatory reaction is currently believed to be largely the result of an interaction between innate immunity (mediated by antigen-presenting cells and natural killer T lymphocytes) and acquired immunity (mediated by T lymphocytes). Psoriasis is a chronic inflammatory systemic disease that affects the skin, nails, and joints. In addition, patients have an increased risk of acquiring certain systemic conditions, such as diabetes mellitus, hypertension, coronary artery disease, metabolic syndrome, and depression [1]. In psoriasis, cutaneous and systemic overexpression of various proinflammatory cytokines has been observed. The cellular composition of the inflammatory infiltrate within the psoriatic plaques, as well as the hyperproliferation of keratinocytes, seems to be influenced by these cytokines. Several recent studies have focused on the relationship between serum levels of inflammatory cytokines in psoriasis patients and clinical parameters such as disease severity. The US National Institutes of Health (NIH) Biomarkers and Surrogate Endpoint Working Group defines a biological biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic intervention. Biological biomarkers include markers for drug effect or response, as well as for diagnosis, prognosis, or physiologic status, such as disease activity or damage not related to drug effect [2].

Biomarkers can provide valuable insights into disease susceptibility and natural history and may serve as surrogate endpoints for a variety of different outcomes. The identification of biomarkers related to comorbidities in psoriasis, such as arthritis, cardiovascular disease, and the metabolic syndrome, has attracted special interest. However, because the development of biomarkers significantly lags behind drug development, the absence of new and appropriate markers may slow the development of patient-tailored targeted therapies.

We discussed the possible use of biomarkers in psoriasis and reviewed the results of several studies of biomarkers in

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the pathogenesis, diagnosis, and treatment of both the inflammatory and dermatologic aspects of psoriatic disease.

2. METHODOLOGY

We searched the Cochrane Central Register of Controlled Trials (Central), Med-Line (PubMed), and Embase databases covering from 1997 to October 2013. We also examined references from selected articles. We included case series with 5 or more patients, cohort trials, and randomized controlled trials. Search terms used were biomarkers, psoriasis, cytokines, chemokines, proangiogenic mediators, growth factors, antimicrobial proteins, neuropeptides, and markers of oxidative stress. We also included some data from our own studies.

3. RESULTS AND DISCUSSION

3.1. General Characteristics of Psoriasis and First Biomarkers

In psoriatic lesions, hyperproliferation and defective terminal differentiation of keratinocytes impair barrier formation; infiltration of activated immune cells leads to inflammation, and interactions between the 2 cell types perpetuate the disease [3, 4]. Transcriptome analyses have revealed approximately 1300 protein-coding genes with altered expression in psoriatic skin [5, 6].

Cytokine interactions (Fig. **1**) [7] in psoriasis have previously been reported, and a linear relationship is

assumed between proximal inducers [interleukin (IL)-23, IL-12, and IL-15], production of interferon (IFN)-α and tumor necrosis factor (TNF) generated by type 1 T cells and dendritic cells (DCs), and downstream activation of numerous IFN-responsive genes through signal transducer and activator of transcription 1 (STAT1) [8]. However, cytokines account for only a small fraction of the more than 1300 protein-coding genes previously mentioned. IFN-α plays a key role in the stimulation and proliferation of T cells and in the formation of psoriatic skin [9]. IL-12 and IL-23 trigger T-helper cell activation and associated downstream responses within the type 1 pathway [10]. IL-23 activates T-helper cells, which subsequently produce IL-17 and IL-22 [11]. IL-15 is a proinflammatory cytokine that induces T-cell proliferation and skin hyperplasia [12]. The high levels of TNF-α, IFN-α, IL-2, IL-6, IL-8, IL-12, and leukemia inhibitory factor (LIF)-1 and the reduced levels of IL-1, IL-4, IL-5, and IL-10 in psoriatic skin lesions suggest that psoriasis is a type 1 immune response disease [13].

Flisiak *et al.* [14] have confirmed an association between plasma IL-18 concentration and psoriasis severity, and have shown that combined measurement of IL-18 and TGF-β1 in plasma can be considered as a possible biomarker of psoriasis activity.

Another study has reported a significant correlation between the extent of skin lesions, psoriasis area severity index (PASI), and IL-18 levels in plasma of patients with psoriasis [15].
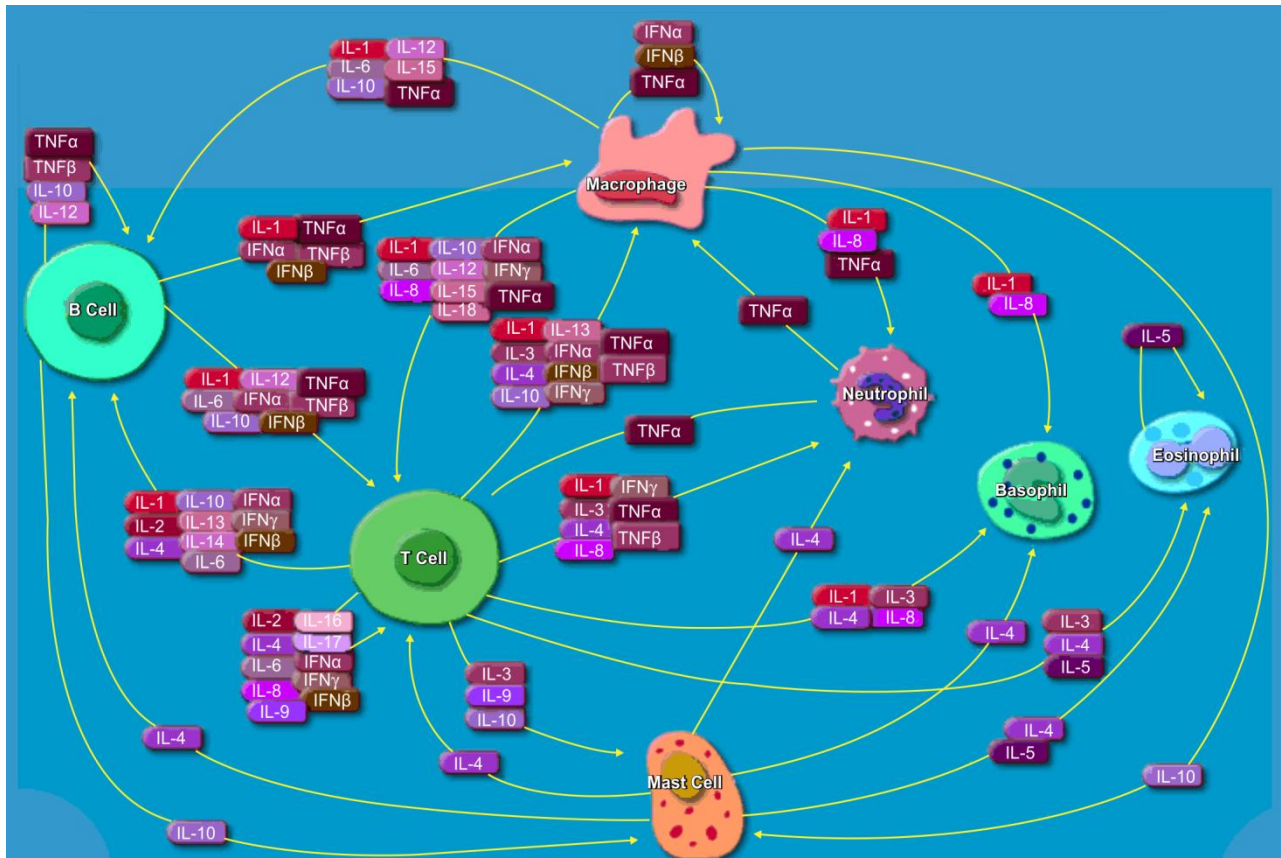

Fig. (1). Metabolic pathway of Cytokines in humans.

The transcription factors STAT1, STAT3, and nuclear factor-κB (NF-κB) are activated in psoriasis. IFNs act as upstream activator for STAT1, and TNF or IL-1 for NF-κB; however, more recently discovered cytokines such as IL-20 and IL-22 also have been found to activate the STAT and NF-κB pathways [16, 17].

Keratinocyte-derived cytokines such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) influence the growth of supporting stromal cells. Activated stromal cells overproduce factors such as keratinocyte growth factor (KGF) that can induce the proliferation of keratinocytes [18]. Many immune-derived cytokines, including IL-1, IL-6, IL-17, IL-19, IL-20, IL-22, TNF, and IFNs, also regulate keratinocyte proliferation, some of which serve as alternative mitogens for this cell type. Antagonism of TNF, IL-12, and/or IL-23 (p40) cytokines with antibodies or fusion proteins can repress the activated pathways [3]. IL-6 contributes to the development of type 2 diabetes [19] and cardiovascular disease [20], IFN-α may be a regulator of atherosclerosis [21], and C-reactive protein (CRP) is a risk factor for cardiovascular disease [22]. IFN-α [23, 24], IL-6 [25, 26], and CRP [27, 28] expression levels are elevated in psoriasis and correlate with disease severity to varying degrees. Rocha-Pereira *et al*. [29] have shown an association of psoriasis with inflammation, as indicated by higher levels of the inflammatory markers such as CRP, haptoglobin, fibrinogen, and C3 and C4, which increase with severity of disease. Rocha-Pereira *et al*.

proposed that haptoglobin and CRP can be used as markers of psoriasis. It has also been proposed that the preferential association between DCs and psoriatic epidermal CD4+ T cells (Fig. **2**) [7] may lead to the stimulation and subsequent clonal expansion of epidermal

CD8+ T cells. Along with CD4+ T cells and DCs, CD8+ T cells are key players in the production of proinflammatory cytokines that have been implicated in psoriasis [30].

Leptin stimulates proinflammatory cytokine release through its effects on the innate and adaptive immune systems; therefore, while leptin serves an important role in infection resistance, overnutrition can contribute to a chronic, proinflammatory state [31, 32]. Another adipose-derived protein, adiponectin, exhibits anti-inflammatory properties and tends to be lower in individuals with psoriasis [33, 34].

Marchetti *et al*. [35] showed that ubiquitous expression of the caspase-cleaved form of the Src tyrosine kinase LYN (v-yes-1 Yamaguchi sarcoma viral related oncogene homolog) induces a skin inflammatory syndrome that recapitulates the main, if not all, features of human psoriasis. An analysis of Lyn expression in human psoriatic skin biopsies showed the presence of a cleaved form of Lyn, which correlates with caspase-1 and caspase-7 activation. The cleavage of caspase-1 has been already reported in human psoriasis biopsies [36]. In addition, Lamkanfi *et al*. [37] established that apoptotic executioner caspase-7 is
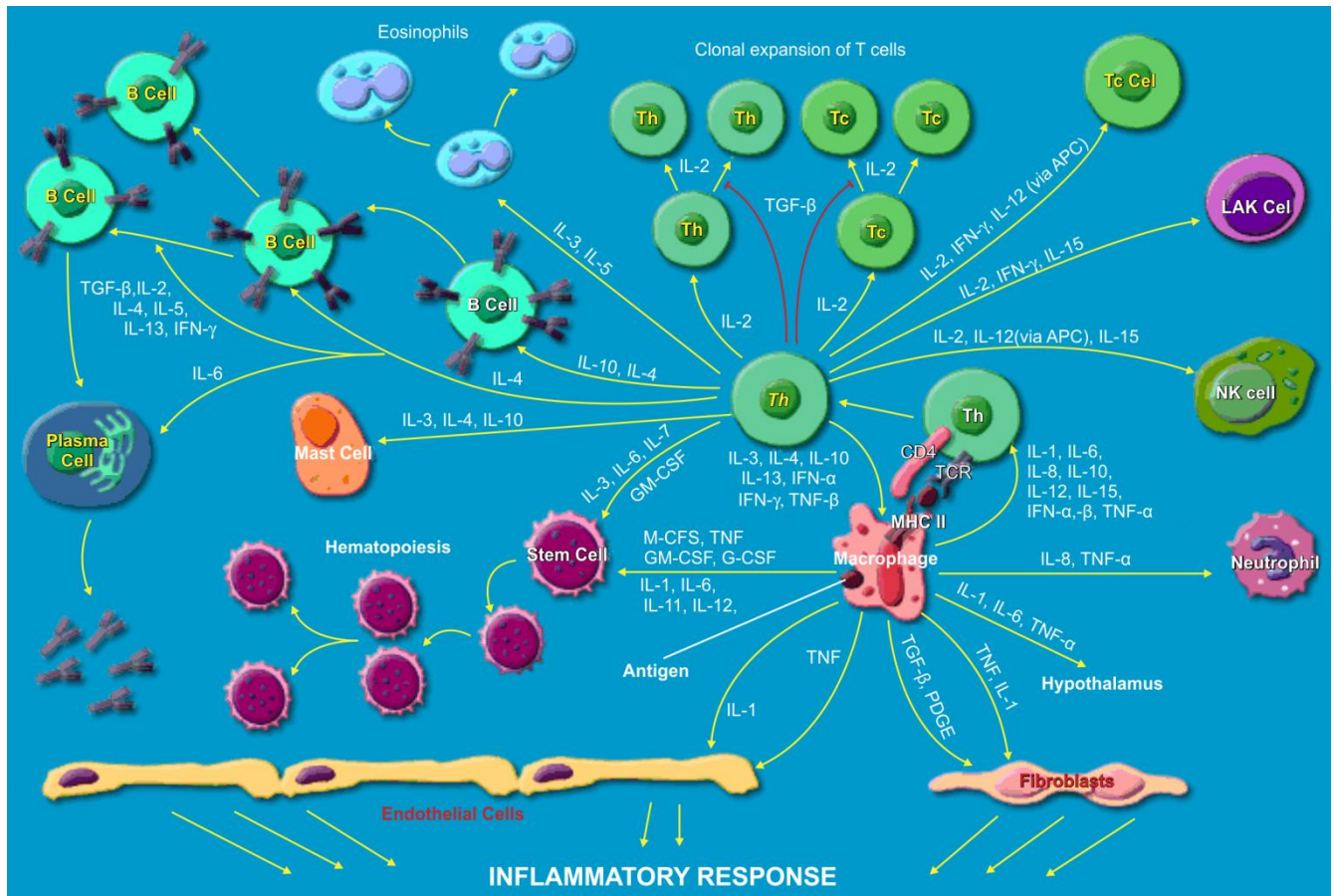

Fig. (2). Metabolic pathway of Inflammatory Response in humans.

directly activated by caspase-1 during an inflammatory process, reinforcing the concept of a cross talk between these 2 classes of caspases. Ayli *et al*. [38] found that Src tyrosine kinases are activated in hyperproliferative epidermal disorders, including psoriasis.

Cells respond to heat shock or stress by producing heat shock proteins (HSPs), which play an important role in the immune and inflammatory responses of the skin, including in psoriasis. One study reported significantly higher expression of HSP60 in guttate and plaque psoriasis than in normal skin. Increased expression of Toll-like receptor 4 (TLR4) has been found in guttate psoriasis, suggesting that TLR4 may be related to the pathogenesis of this disease [39]. HSP27-induced synthesis of IL-12 in immature DCs has also been reported [40].

Gisondi *et al*. [41] found that serum levels of chemerin, resistin, and CRP were significantly higher in patients with chronic plaque psoriasis compared with controls and this was independent of age, sex, body mass index, and metabolic comorbidities. Further, there is a linear correlation between resistin, chemerin, and CRP. Chemerin levels were higher in patients with psoriatic arthritis (PsA) than in those without PsA. Chemerin was linearly correlated with CRP and resistin, but not with psoriasis severity as measured by PASI or body surface area. Chemerin is primarily a chemotactic protein that recruits macrophages and plasmocytoid DCs expressing the ChemR23 receptor at sites of inflammation [42]. Some chemerin isoforms may exert anti-inflammatory activities [43]. Chemerin is crucial for the recruitment of plasmocytoid DCs in the early phase of developing psoriatic lesions, and it is mostly released by dermal fibroblasts and activated by neutrophil-derived elastases [44]. On the other hand, resistin is an adipokine initially related to insulin resistance in rodents. High plasma levels of resistin have been associated with endothelial dysfunction, proatherogenic inflammatory markers, and increased cardiovascular risk [45]. CRP elevation is associated with psoriasis inflammation because CRP levels decrease when psoriasis is successfully treated. This has been observed after treatment with narrow-band ultraviolet B (UVB), cyclosporine, and anti-TNF-α agents [46]. Last, visfatin is a novel 52-kDa adipokine that shows insulin-like effects and has been associated with atherosclerosis and plaque destabilization [47]. It is a proinflammatory cytokine, produced by macrophages in visceral adipose tissue, that up-regulates the production of IL-6, IL-1β, and TNF-α in human monocytes [48]. Visfatin gene expression is increased both in psoriatic skin samples and in peripheral blood cells of severely affected psoriasis patients [49]. Visfatin was found to be higher in patients than in controls and, unexpectedly, to increase after infliximab therapy. Tilg and Moschen [50] proposed that at higher concentrations, visfatin can also induce the expression of anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonists. Therefore, increased visfatin level could exert an anti-inflammatory effect.

According to the National Institutes of Health Biomarkers Definitions Working Group, a biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention". Biomarkers can be divided into three categories: type 0 biomarkers, that correlate longitudinally with the severity of the disease; type I biomarkers, that reflect the effect of an intervention according to the mechanism of action of the therapy itself; and type II biomarkers, that are surrogate endpoints for a therapy They can be represented by soluble, cellular, tissue-associated, or genetic markers. We summarized the most important biomarkers in Table **1** [51].

3.2. Biomarker Selection Using Genomic and Transcriptomic Tools

Quekenborn-Trinquet *et al*. [52], using cDNA array and kinetically monitored reverse transcriptase polymerase chain reaction (RT-PCR), compared the gene expression profiles of plaque psoriasis at different anatomical sites for both symmetrical and asymmetrical diseases. They identified 3 novel psoriasis markers, namely SPRR2C (a marker of abnormal keratinocyte differentiation), MX2 (transcription factor involved in mediating the proinflammatory effects of IFN-γ), and CYC1 (belonging to cytochrome c family), indicating the high energy requirement of highly proliferating epidermis of psoriatic lesions and transcriptional deregulation of proapoptotic factors [53]. A statistically based meta-analytic approach systematically combines microarray studies from different patient populations and laboratories to provide a single estimate of the overall differential expression level for each gene. In particular, a meta-analysis was conducted on 5 microarray data sets, namely, Meta-Analysis Derived (MAD) transcriptome, including 193 pairs from lesional (LS) and nonlesional (NL) skin of psoriasis patients [54]. The MAD-3 transcriptome was obtained from patients with "plaque-type," "chronic," and "moderate to severe" psoriasis, while the MAD-5 study also included patients with "mild to severe" disease, suggesting that these results represent the transcriptome from a range of severity with broad applicability across the many types of this disease. In the MAD-5 transcriptome, 677 genes were up-regulated and 443 genes were down-regulated in LS skin compared with NL skin. In the MAD-3 transcriptome, a greater number of differentially expressed genes were found (1084 up-regulated and 748 down-regulated). Analysis of differentially expressed genes, obtained using Ingenuity Pathway Analysis software, identified several key cytokine pathway genes (e.g., IL-17 and IFN-α) and other important genes such as those involved in the atherosclerosis signaling and fatty acid metabolism pathways. The overall importance of IL-17 signaling in psoriasis is highlighted by several recent studies in which major improvements in psoriasis were seen in clinical trials using IL-17 antagonists [55-57]. However, the largest difference detected in profiles extracted from Ingenuity software of the MAD-3 transcriptome was in the atherosclerosis signaling pathway. This association is of interest in light of the well-established link between moderate-to-severe psoriasis and a significantly increased risk of cardiovascular disease [58-60]. In addition, MAD-3 list identified several up-regulated genes, such as protein tyrosine phosphatase non-receptor type 22 (*PTPN22*), which is a psoriasis risk gene with polymorphisms associated with

Table 1.　Biomarkers in Psoriasis

Different Categories of Biomarkers in Psoriasis			
Biomarkers and Biological Sample	**Name/Function**	**Associated Disease (Clinical Use)**	**Clasification (Types)**
Tissue associated			
K1, K6, K10, K16	Keratins	Psoriasis	0
VEGF	Vascular endothelial growth factor	Psoriasis	0, 1
S100A8/A9	S100 calcium-binding proteins	Psoriasis	0
IL-6	Proinflammatory cytokines	Psoriasis	0
IL-8		Psoriasis	0
IL-18		Psoriasis	0
TNF-α		Psoriasis	0
IFN-γ	Th1 y Th17 cytokines	Psoriasis	0, 1
IL-17		Psoriasis	0, 1, 2
IL-22		Psoriasis	0
TLR4	Toll-like receptor 4	Guttate psoriasis	?
Oxidative stress markers (eg, oxidised LDL)	Lipid peroxidation	Psoriasis/PsA	0
Src tyrosine kinase LYN	LYN (v-yes-1 Yamaguchi sarcoma viral related oncogene homolog) Caspase-1 and caspase-7 activating	Psoriasis/PsA	0, 2
Soluble biomarkers			
Serum/plasma			
CRP	C-reactive protein, acute-phase reactant	Psoriasis/PsA	0, 2
Chemerin	Chemotactic protein in inflamatory response	Psoriasis/PsA	0, 2
ESR	Erytrocyte sedimentation rate	Psoriasis	0, 1, 2
VEGF	Vascular endothelial growth factor	Psoriasis	0
hBD-2	β-defensin-2	Psoriasis	0
S100A8/A9	S100 calcium-binding proteins	Psoriasis	0
IL-6	Proinflammatory and chemotactic cytokine	Psoriasis/PsA	0
IL-8		Psoriasis	0
IL-18		Psoriasis	0
TNF-α		Psoriasis	0
IFN-γ	Th1/Th17 cytokines	Psoriasis	0, 1
IL-17		Psoriasis	0, 1, 2
IL-22		Psoriasis	0
TGF-β1	Transforming growth factor-β1	Psoriasis	0
Leptin	Adipokines, proinflammatory functions	Psoriasis	0
Resistin		Psoriasis	0
Cell subsets			
Th1	T helper subsets	Psoriasis	0

Table 1 Contd....

Different Categories of Biomarkers in Psoriasis			
Biomarkers and Biological Sample	**Name/Function**	**Associated Disease (Clinical Use)**	**Clasification (Types)**
Th17		Psoriasis	0
Th22		Psoriasis	0
NKT cells	Natural killer T cells	Psoriasis	0
Genetic markers		Psoriasis	?
PSORS4 S100	S100 calcium-binding proteins	Psoriasis	?
CNVDEFB4	β-defensin-2	Psoriasis	?
SNPs *Il23r*	Proinflammatroy cytokines	Psoriasis	?
SNPs *Il23a*		Psoriasis	?
SNPs TNF-α encoding gene promoter		Psoriasis/PsA	?

Abbreviation: ? not included ; SNP, single-nucleotide; IL, interleukin; PsA, psoriatic arthritis

early-onset psoriasis, and cytochrome b5 reductase 2 (*CYB5R2*), which is involved in fatty acid metabolism. Several genes were also found to be down-regulated, including transmembrane protease serine 11E (*TMPRSS11E*), also called DECS1 [52]. TMPRSS11E expression is correlated with normal keratinocyte differentiation [61], and thus its reduction is consistent with the loss of normal keratinocyte differentiation that occurs in psoriasis. BTB and CNC homology 1, basic leucine zipper transcription factor 2 (*BACH2*) has been implicated as a type 1 diabetes risk factor by genome-wide association study [62], and may have a role in the response to viral antigens [63]. C-mer proto-oncogene tyrosine kinase (*MERTK*) may play a role in the clearance of apoptotic cells by antigen-presenting cells [64] or may act as an anti-inflammatory agent, potentially inhibiting unrestrained TLR activation [65]. Polymorphisms of peroxisome proliferator-activated receptor

γ (PPARγ) have been found in a cohort of psoriatic arthritis [66]. PPARβ/δ activation, which can be antagonistic to PPARβ, has been observed in psoriatic skin [67], and activation of PPARβ/δ was shown in a psoriasis-like mouse model of disease [68]. High expression levels of the above-mentioned genes were all confirmed by RT-PCR (Table **2**).

Among classifier genes, *TCN1* (transcobalamin 1/HAPTOCORRIN) anchors are consistently closely related to LS skin across different studies. This gene encodes a member of the vitamin B12-binding protein family, cobalamin metabolic process, which is found in neutrophilic granules. TCN1 has shown linkage to serum insulin concentrations in impaired glucose tolerance [69]. TCN1 protein was also increased in the synovium of rheumatoid arthritis [70] and was significantly associated with cholesterol levels or statin response [71], which may provide a predisposing link between skin inflammation and high

Table 2. **Biomarkers Differentially Expressed in Psoriasis Patients Compared with Both Non Lesional Skin**

Psoriatic Skin	**Non Lesional Skin**
SPRR2C (A marker of abnormal keratinocyte differentiation)	
MX2 (transcription factor involved in mediating the proinflammatory effects of IFN-γ)	
CYC1 (belonging to cytochrome C family	TMPRSS11E expression (is correlated with normal keratinocyte differentiation)
PPARβ/δ (Polymorphisms of peroxisome proliferator-activated receptor)	
TCN1 (transcobalamin 1/HAPTOCORRIN)	
KYNU (Kynureninase) MUC7 (Mucin 7) CLDN8 (Claudin 8)	Etanercept "molecular scar" Driving the good evolution of disease
(S100A12) (S100 calcium binding protein A12)	
SERPINB3 (Serpin peptidase inhibitor clade B member 3)	
KNYU (enzyme involved in the biosynthesis of nicotinamide adenine dinucleotide (NAD) cofactors from tryptophan through the kynurenine pathway)	

cholesterol. Several genes in the psoriasis classifier, kynureninase (*KYNU*), mucin 7 (*MUC7*), and claudin 8 (*CLDN8*), were part of the etanercept "molecular scar" previously reported by Suárez-Fariñas *et al*. [72]. The molecular scar represents a group of genes that are still expressed at the end of 12 weeks of successful treatment with etanercept, an anti-TNF agent used for psoriasis, at the time point where there was complete clinical resolution and no visible skin inflammation. KYNU is an enzyme involved in the biosynthesis of nicotinamide adenine dinucleotide (NAD) cofactors from tryptophan through the kynurenine pathway. Robertson *et al*. [73] have recently identified several genes in the classifier as top genes harboring differential methylation sites in psoriasis versus normal skin, namely, S100 calcium binding protein A12 (*S100A12*), serpin peptidase inhibitor clade B member 3 (*SERPINB3*), and *KNYU*. The *S100A12* gene is a highly inflammatory molecule that binds to the receptor for advanced glycation end products (RAGE) and is increased in inflammatory DCs and keratinocytes in response to inflammatory cytokines such as IL-17, TNF-α, and IFN-α [74, 75]; it exhibited the largest increase in expression.

Suárez-Fariñas *et al*. [59] conducted a gene set enrichment analysis and obtained results similar to those of previous reports [5, 76, 77]. Suárez-Fariñas *et al*. [59] and Gudjonsson *et al*. [78] reported 15 genes showing highly differential expression patterns, including up-regulated genes such as *S100A12*, *SERPINB4/SERPINB3*, and *IL-8* and down-regulated genes such as betacellulin (*BTC*), WNT inhibitory factor 1 (*WIF1*), thyroid hormone responsive (*THRSP*), and WD repeat domain 72 (*WDR72*). Suárez-Fariñas *et al*. [59] have also confirmed many up-regulated genes involved in signaling pathways believed to be central in psoriasis pathogenesis, including the IFN-α, TNF-α, and IL-17 signaling pathways. Some of the specific up-regulated genes include 2′-5′-oligoadenylate synthetase-like (*OASL*), chemokine C-X-C motif ligand 1 (*CXCL1*), *STAT1*, and myxovirus resistance 1 (*MX1*) belonging to the IFN-α signaling pathway; aldo-keto reductase family 1 member B10 (*AKR1B10*), IL-1 family member 9 (*IL1F9*), and *CXCL9* belonging to the TNF signaling pathway; and chemokine C-C motif ligand 20 (*CCL20*) and *IL-8* belonging to the IL-17 signaling pathway [79, 80]. Another identified gene was renin (*REN*), which is involved in the renin-angiotensin signaling pathway that ultimately leads to aldosterone release, vasoconstriction, and an increase in blood pressure, thus suggesting the involvement of this gene in the enhanced plasma renin activity and increased urinary aldosterone excretion observed in psoriatic patients [81]. Cytotoxic T-lymphocyte-associated protein 4 (*CTLA4*) gene, listed under metabolic disorder and diabetes in the metabolic disease functional pathway, is involved in negative regulation of T-cell proliferation as well as regulatory T-cell differentiation and immune response. In psoriasis-like murine skin, the induction of T-regulatory cells involving CTLA4 signaling is one of the mechanisms for the therapeutic action of psoralen plus long-wave UV, a well-established psoriasis treatment [82]. TLR3 has a fundamental role in pathogen recognition and activation of innate immunity and it is expressed in the keratinocytes of normal, nonlesional, and psoriatic skin and in monocyte-derived DCs [83]. The interaction of TLR3 with its ligand can result in keratinocyte activation and the release of proinflammatory cytokines TNF-α and IL-8 [84], and TLR3 signaling generally activates numerous IFN- and TNF-stimulated gene products that are also up-regulated in psoriasis. However, because of the extensive overlap in regulated genes, activation of signaling by TLR3 cannot be definitively determined.

IL-12/IL-23 has been shown to be involved in psoriasis. The activation of IFN-α signaling in lesional skin of psoriatic patients has been confirmed by genomic profiling [5]. Increased expression of mRNAs encoding the p19 and p40 subunits of IL-23 has been found in lesional skin of psoriatic patients [85, 86], showing that IL-1β was constitutively expressed by keratinocytes *in vivo* and overexpressed in lesional skin. Boniface *et al*. [87] demonstrated that oncostatin M (OSM), a member of the IL-6 family of cytokines, was a potent keratinocyte activator similar to TNF-α, IL-1, IL-17, and IL-22. They also showed that OSM was associated with cutaneous inflammatory responses. IL-22, an effector cytokine mainly produced by T cells, and IL-17 were found to mediate cross talk between the immune system and epithelial cells and might have essential functions in host defense and the pathogenesis of psoriasis [12].

Yao *et al*. [77] conducted a large-scale study, using Affymetrix® whole genome U133 plus v2.0 array platform, to profile a large panel of paired lesional and nonlesional skin biopsies from psoriatic patients. They showed that (i) mRNAs of type I IFN family members are up-regulated in lesional skin but not in nonlesional skin (except IFN-a5 and IFN-k); (ii) the IFN-α/β signaling pathway is the most significantly activated pathway in lesional skin compared with both nonlesional skin and skin from healthy donors; (iii) there is a prevalent and robust overexpression of a large panel of type I IFN-inducible genes in lesional skin (but not in nonlesional skin) of the majority of the psoriatic patients examined in the study; (iv) plasmacytoid DCs, which are natural IFN-α/β–producing cells, are present in lesional skin; and (v) IFN-stimulated gene 15 ubiquitin-like modifier (ISG15) and STAT1, STAT2 type I IFN–inducible proteins are overexpressed in lesional skin of psoriatic patients. Of the type I IFN-inducible genes overexpressed in lesional skin of psoriatic patients, STAT1 is a key component in forming the IFN-stimulated gene factor 3 (ISGF3) complex. ISGF3 is a heterotrimeric transcriptional factor complex that is formed upon the activation of the type I IFN receptor. It is composed of phosphorylated STAT1, STAT2, and IFN regulatory factor [88]. Upon translocation to the nucleus, ISGF3 activates the transcription of type I IFN–inducible genes [89]. IRF7 is the master regulator of the IFN-α/β–mediated immune response, and myeloid differentiation primary response 88 (MYD88) and IRF7 regulate the induction of CD8+ T cell responses [90, 91]. IRF1 functions as a transcriptional activator of type I IFN–inducible genes [90]. MX1, MX2, and the 2′-5′-oligoadenylate synthetase (OAS) family members OAS1, OAS2, and OAS3 mediate resistance to virus infection. ISG15 is a ubiquitin-like protein that is conjugated to many cellular proteins upon activation by IFN-α/β [92]. Ubiquitin-specific peptidase 18 (USP18), ubiquitin-conjugating enzyme E2L 6 (UBE2L6), and HECT and RLD

domain containing E3 ubiquitin protein ligase 5 (HERC5) are all members of the ISG15 signaling pathway. Lysosomal-associated membrane protein 3 (LAMP3) and cluster of differentiation 83 (CD83) are DC marker genes.

Yao *et al.* [76] also showed that the mRNAs of TNF-α and TNF-α–inducible genes are overexpressed in lesional skin of psoriatic patients, and observed enrichment of myeloid DCs and CD4$^+$ T cells, as well as overexpression of IFN-α–inducible genes, in lesional skin of psoriatic patients. The mRNAs for IL-8 (a key chemoattractant for neutrophils) and IFN-α and TNF-α–inducible genes were not overexpressed in nonlesional skin compared with skin from healthy donors, whereas the same genes were overexpressed in lesional skin in a similar manner to the overexpression of mRNAs of type I IFN family members and type I IFN–inducible genes.

Another strategy was used by Nair *et al.* [93] by genotyping 438,670 single-nucleotide polymorphisms (SNPs) in 1409 European-ancestry psoriasis cases and 1436 controls. Psoriasis susceptibility has a genetic component, partly explained by the association between psoriasis and major histocompatibility complex (MHC) haplotypes bearing HLA-Cw6 [94] and SNPs near IL12B and IL23R3. Nair *et al.* [92] found that loci with confirmed association encode human leukocyte antigen-C α chain (*HLA-C*); *IL23A, IL23R,* and *IL12B,* which are genes involved in IL-23 signaling; TNF-α-induced protein 3 (*TNFAIP3*) and TNFAIP3-interacting protein 1 (*TNIP1*), genes that act downstream of TNF-α and regulate NF-κB signaling; and *IL4* and *IL13,* which are genes involved in the modulation of T-helper 2 immune responses [95].

3.3. Epigenetics Unveils New Biomarkers

Epigenetic mechanisms have thus recently emerged as a new putative link between genetic and environmental factors in the pathogenesis of psoriasis. These mechanisms include DNA methylation, histone modifications, as well as microRNA (miRNA) dysfunctions [96]. In mammalian cells, DNA methylation is catalyzed by DNA methyltransferases (DNMTs) with *S*-adenosyl-methionine as the methyl donor, and takes place almost exclusively at the 5′-carbon position of cytosine residues within CpG pairs. In humans, 3 DNMT genes, *DNMT1, DNMT3a,* and *DNMT3b,* establish and maintain DNA methylation patterns [97]. Methylation-sensitive genes implicated in the pathogenesis of lupus are aberrantly expressed in patients with psoriasis. The expression of genes such as *perforin* and the T-cell integrin leukocyte function-associated antigen-1 (*LFA-1*) was increased in the epidermis of psoriatic lesions [98, 99]. On the other hand, the promoter regions of *CDKN2B* (cyclin-dependent kinase inhibitor 2B; also known as p15) and *CDKN1A* (also known as p21) genes are hypomethylated in psoriasis, and colony counts of high-proliferative potential colony-forming cells (HPP-CFCs) in the bone marrow of patients with psoriasis are significantly lower than those of healthy controls [100]. In addition, the low colony formation of HPP-CFCs from bone marrow hematopoietic progenitor cells in psoriatic patients is closely correlated with the promoter methylation levels of the cyclin-dependent kinase inhibitor 2A (*CDKN2A,* also known as *p16*) gene in HPP-CFCs cells [101]. Methylation of the *p16^{INK4a}* gene promoter has been observed in 30% of patients with psoriasis, for whom disease activity (as measured using PASI score) was higher than in patients who did not exhibit *p16^{INK4a}* methylation. In addition, p16^{INK4a} mRNA expression in the methylated group was significantly lower than that in the unmethylated group [102]. *p14^{ARF}*, a gene homologous to *p16^{INK4a}*, was also hypermethylated in psoriatic skin lesions, resulting in down-regulation of p14^{ARF} [103]. Aberrant DNA methylation was also observed in the *SHP-1* gene, which serves as a regulator of cell growth and proliferation and possesses 2 promoters. The *SHP-1* promoter 2 region was found to be significantly demethylated in keratinocytes from psoriatic lesions [104].

One of the best studied histone modifications is acetylation, which is the transfer of an acetyl group from acetyl coenzyme A to the lysine side chain in the acceptor histone, catalyzed by histone acetyltransferases (HATs). Histone acetylation occurring at specific loci results in an open chromatin state, allowing transcription factors access to DNA strands. Two highly homologous HATs, E1A binding protein P300 and cAMP-response element binding protein (CBP), as well as P300/CBP-associated factor (PCAF), form a large protein complex that has been proved to play critical roles in diverse cell processes, ranging from muscle differentiation to cancer [105]. Histone deacetylase 1 (HDAC1), a member of class I histone deacetylases, plays critical roles in cellular senescence, aging of the liver, myelination, and adult neurogenesis [106]. In addition, overexpression of the mRNA for HDAC1 was observed in psoriatic skin compared with skin from normal controls [107]. Silent mating type information regulation 2 homolog 1 (SIRT1) is a nicotinamide adenine dinucleotide (NAD$^+$)-dependent deacetylase involved in the process of gene expression, cellular metabolism, and cellular stress responses [108]. Recently, SIRT1 has been demonstrated to regulate keratinocyte proliferation and differentiation *in vitro*. In normal human keratinocytes, SIRT1 serves to inhibit proliferation and promote differentiation [109]. Zhang *et al.* [110] measured the global acetylation/methylation level of total histones in peripheral blood mononuclear cells (PBMCs) from patients with psoriasis vulgaris and healthy controls. They reported that, compared with normal controls, PBMCs from psoriatic patients' exhibit histone H4 hypoacetylation accompanied by up-regulated mRNA expression of HDAC1 and down-regulated expression of P300, CBP, and SIRT1. This study reports that the histone code is impaired in psoriasis vulgaris. Moreover, the mRNA expression level of SIRT1 is decreased in psoriatic patients' PBMCs compared with normal controls, suggesting that proliferation of keratinocytes in psoriasis results from decreased SIRT1 expression.

Methylation of histone lysine and arginine is associated with both active and inactive transcription. Lysine 4, 9, 27, 36, and 79 of histone H3 (H3K4, H3K9, H3K27, H3K36, and H3K79) and lysine 20 of histone H4 (H4K20) are the most commonly methylated loci to form mono-, di-, and tri-methylation. SUV39H1 and SUV39H2 are the 2 enzymes responsible for H3K9 trimethylation, and H3K27 methylation is catalyzed by the Enhancer of zeste E(z) and its mammalian *Drosophila* protein homologue enhancer of

zeste homolog 2 (EZH2), a member of polycomb group proteins associated with cell proliferation and cell cycle regulation) [111, 112]. In the study carried out by Zhang *et al*. [109], global H3K4 and H3K27 methylation levels did not exhibit significant differences between patients with psoriasis vulgaris and healthy controls, but SUV39H1 and EZH2 mRNA levels were both found to be up-regulated in psoriatic patients compared with normal controls, leading to the hypothesis that up-regulation of EZH2 plays certain roles in the pathogenesis of the disease.

MiRNAs are a class of short, regulatory RNAs that play critical roles in human development and disease pathogenesis [113-115]. MiRNA binding may result in translational repression or destabilization of the transcript, although it is still unclear which mechanism is dominant in metazoans [116, 117]. Joyce *et al*. [118] identified 80 known and 18 novel miRNAs that were differentially expressed by a fold change of 2 or more in involved or uninvolved psoriatic skin versus normal skin. The authors observed widespread expression of isomiRs (miRNA isoforms that differ at the 3′ or 5′ ends because of imperfect enzymatic processing) and other subproducts derived from known and novel miRNA loci and a low frequency of miRNA editing in both normal and psoriatic skin. These differentially expressed miRNAs are likely to influence many processes that are involved in psoriasis pathogenesis such as angiogenesis (miR-21, miR-31, miR-378), epidermal differentiation (miR-135b, miR-205, miR-203-AS), and inflammation (miR-142-3p). miR-142-3p displayed strong immunostaining, which is consistent with the previously described expression of miR-142-3p in hematopoietic tissues [119] and supporting a role in epidermal inflammation in psoriatic lesions. Other miRNAs that are abnormally expressed in psoriasis are miR-146a and miR-125b. Overexpression of miR-146a in psoriasis is controlled by the transcription factor NF-κB, and the NF-κB target genes *TRAF6* and *IRAK* are involved in regulating the TNF-α signaling pathway [120, 121], suggesting that miR-146a may control TNF-α signaling in the skin. Unlike miR-146a, miR-125b targets TNF-α directly for posttranscriptional repression and decreases its expression in psoriasis [122]. It is therefore believed that down-regulation of miR-125b may be associated with TNF-α overproduction in the process of skin inflammation. A novel interaction was identified between miR-221/2 and TIMP3, which may play an important role in the pathogenesis of psoriasis [123]. Another study [124] lends support that miR-142-3p/-5p, miR-146a/b, and miR-155 are likely to play a role in psoriasis. MicroRNA-155 is expressed in monocytes and macrophages acting as an inflammatory mediator [120, 124], and it has been reported that TNF-α stimulates miR-155 expression in synovial fibroblasts [125]. Furthermore, miR-155 is involved in a positive feedback loop in TNF-α production [126]. Further, Zibert *et al*. [123] have selected 4 more miRNAs, that is, miR-22, miR-24-1, miR-498, and miR-551a, that were down-regulated in involved and uninvolved psoriatic skin compared with healthy skin, pointing to a central role of these miRNAs in the skin of patients diagnosed with psoriasis, but further studies are necessary to know about its specific ontology.

Sonkoly *et al*. [127, 128] found that up-regulation of miR-203 in psoriatic plaques was concurrent with the down-regulation of an evolutionarily conserved target of miR-203, suppressor of cytokine signaling 3 (SOCS-3), which is involved in inflammatory responses and keratinocyte functions. SOCS-3 deficiency leads to sustained activation of STAT3 in response to IL-6 [129], a cytokine present in the psoriatic lesions [5]. This suggests that the suppression of SOCS-3 by miR-203 in psoriatic lesions would in turn lead to constant activation of STAT3. Indeed, the psoriatic hyperplastic epidermis shows increased STAT3 activation, and constitutively active STAT3 in keratinocytes leads to the spontaneous development of psoriasis in transgenic mice [130]. Thus, the up-regulation of miR-203 may have important implications for psoriasis pathogenesis by preventing the up-regulation of SOCS-3 in response to cytokines. In addition to the modulation of inflammatory responses, SOCS-3 has also been implicated in the regulation of keratinocyte proliferation and differentiation. Overexpression of SOCS-3 has been shown to lead to final differentiation of keratinocytes and inhibit serum-stimulated proliferation of the cells [131]. MiRNA-mediated suppression of SOCS-3 expression in keratinocytes may therefore not only modulate cytokine signaling but also contribute to keratinocyte hyperproliferation and alteration in keratinocyte differentiation in psoriatic plaques.

3.4. A Step Beyond: Proteomics

Two low-molecular-weight proteins strongly up-regulated in psoriatic skin that were proven to be partially released by cells [132], "psoriasin" [133] and psoriasis-associated fatty acid-binding protein (PA-FABP) [134], point to a dysregulated fatty acid metabolism in psoriatic cells.

Plavina *et al*. [135] focused their investigations on plasma from psoriatic patients by using a combination of proteomics and peptidomics to detect increased concentrations of cytoskeletal proteins and their fragments in psoriatic plasma. Their results suggested disease-related cell leakage of these proteins and their increased proteolysis. Moreover, the authors found increased concentrations of 2 proteins that play a role in genetic predisposition to psoriasis and in keratinocyte differentiation: calgranulins A and B. On this basis, they hypothesized that the overproduction of calgranulins may alter calcium homeostasis in the epidermis and lead to altered relocalization of cytoskeleton components and their abnormal proteolysis, as well as to immune responses against circulating cytoskeletal proteins. Another striking finding was a decrease in fibrinogen fragments, suggesting a possible involvement in autoimmunity and inflammation and leading the authors to hypothesize a link between altered proteolysis of fibrinogen due to changes in its PTM and the development of psoriatic arthritis [136].

Ryu *et al*. [136] reported that the proteome of lesional psoriatic skin lesions (LP) indicates the up-regulation of proteins involved in the regulation of cell death (apoptosis), defense response, and inflammatory response. Of particular interest, increased expression of glutathione *S*-transferase 1 (GSTP1) and peroxiredoxin 2 (PRDX2), which are involved in the Redox balance system, and stratifin (SFN), which is involved in the cellular proliferation system [137], was observed in psoriatic lesional skin. Expression of PRDX2, SFN, and GSTP1 led to an increase in LP, compared with

normal skin (N) and nonlesional psoriatic skin lesions (NP). Elevated levels of SFNs enforce G_2/M cell cycle arrest by sequestration of cell division control protein 2 homolog Cdc2/cyclin B1 complexes in the cytoplasm and are required for a stable G_2/M arrest after DNA damage [138, 139].

Reactive oxygen species (ROS), acting as second messengers, influence cellular signal transduction pathways such as proinflammatory signaling pathways. The most significant effects are observed in the MAPK/AP-1, NF-κB, and JAK-STAT signaling pathways, which have been regarded as early events in the inflammatory process in psoriasis [140-142]. In skin lesions, massive infiltration of various leukocyte populations in an activated state certainly leads to local release of a number of pro-oxidative species, which, in turn, are implicated in proinflammatory activation of the resident cells of the skin, particularly, keratinocytes and fibroblasts. Increased PRDX2 and GSTP1 may play a role in reduction of ROS-stress in cells, thereby preventing cells from ROS-induced DNA damage or cell death [137].

Another marker, receptor for advanced glycation end products, is abundant in both keratinocytes and leukocytes, although normally, its expression is low [143]. RAGE participates in a range of processes in these cell types, including inflammation. It is being investigated as a drug target for treatment of various inflammatory disorders [144]. Piruzian *et al*. [145] proposed that RAGE can also play a significant role in psoriasis. They have also identified a total of 10 proteins that were overabundant at least 2-fold in lesional skin compared with uninvolved skin: keratin 14, keratin 16, keratin 17, squamous cell carcinoma antigen, squamous cell carcinoma antigen-2, enolase 1, superoxide dismutase [Mn], salectin-7, S100 calcium-binding protein A9, and S100 calcium-binding protein A7. Several of these proteins were previously reported to be overabundant in psoriatic plaques [146-149].

CONCLUSIONS

In conclusion, psoriasis is a common, chronic, recurrent skin disorder characterized by keratinocyte proliferation, T-cell activation, and angiogenesis. In recent years, many studies have been conducted on psoriasis biomarkers related to diagnosis, pathogenesis, prognosis, or therapeutic response.

In psoriatic disease, biomarkers could be relevant for distinction between the different clinical variants of the disease, for assessment of disease activity and severity, and for prediction of the outcome of a therapeutic intervention. Biomarkers could also allow the selection of patient-tailored therapy to maximize the beneficial effect.

A field of great importance is the use of biomarkers for prediction of development of comorbidities such as arthritis, cardiovascular disease, and metabolic syndrome. Finally, biomarkers can also provide insights into the mechanisms involved in the pathogenesis of the disease. So far, there are limited validation data to support the use of candidate biomarkers in clinical practice for diagnosis, assessment of disease activity, or the prognosis of psoriatic disease. A number of biomarkers have been investigated, and as we mentioned earlier, some of them are promising but they need

further replication and validation. Novel biomarkers await discovery. In future, biomarkers for disease activity, response to therapy, and joint damage progression need to be identified so that management of patients with psoriasis may be optimized. As dermatology advances toward personalized medicine, microarrays and related "omics" techniques will be directly applicable to the personalized treatment of psoriasis. The major concern for validation is the lack of quality control and insufficient statistical analysis, so there is a need for standards to develop validation criteria for biomarker selection

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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