

## Proteomics in Psoriasis: Recent Advances

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**Abstract.** *Psoriasis continues to affect a large percentage of patients worldwide and strongly appears to be a systematic disease. Efforts are being made to understand its etiology, which have led to research extended to genomic analysis with a focus on the role of pro-inflammatory cytokines, which play a major role in the pathogenesis of the disease. Plasma proteomic analysis in various diseases has provided promising results for choosing the right treatment for psoriasis, suggesting that it could play a key role in the prevention, prognosis, and treatment of the disease by individualizing treatment choices based on the proteomic profile of each patient. In this review, we focus on existing data in the bibliography on proteomic analysis in psoriasis and relevant approaches to future targeted therapies.*

Psoriasis remains a chronic inflammatory condition of the skin and joints. It is estimated to affect millions of people worldwide; however, its aetiology has still not been fully elucidated. Apparently, it is a multifactorial disease influenced

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by exogenous and endogenous factors, which define the clinical symptoms, signs, and severity of the disease (1).

The incidence of this condition in Caucasian children has significantly increased over time, with the chronic plaque type appearing to dominate (73.7%). The extremities (59.9%) and the scalp (46.8%) are the most affected sites. The incidence of the disease increases with age; however, it is not different between both sexes (2). A recent German study showed a rise in incidence in men compared to women, peaking in midlife, and declining from the age of 60, in both sexes (3). It seems that the annual incidence of this disease has increased in the last 40 years for unknown reasons; changes in the diagnostic patterns developed recently could be one factor (4). It is important to note that, psoriasis ranks second in the list of diseases associated with depression (5).

Many studies have investigated psoriasis and its role in the systemic comorbidities such as: cardiometabolic diseases (6, 7), gastrointestinal diseases (8, 9) chronic kidney disease (CKD) (10), malignancy (11), infection (12, 13), mental health issues (14, 15), and psoriatic arthritis (PsA) (16). Severe psoriasis is associated with an increased risk of death, primarily due to cardiovascular events (17). Overweightness and obesity, more common among psoriatic patients, increase the severity the disease (18). In 1961, Reed *et al.* first investigated the high prevalence of thrombosis or myocardial infarction (MI) in necropsy material from psoriatic arthritis patients (19). During the last decades, there has been increasing epidemiological evidence supporting the identification of more systemic diseases as extracutaneous medical conditions related to psoriasis. For example, eye manifestations and complications can be seen in psoriasis arthritis patients, symptoms usually not investigated by physicians (20, 21). There is an increasing prevalence of comorbidities associated with psoriasis on a global scale



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(21), suggesting that it is not solely a skin disease; therefore, investigators should focus on treatments beyond topical agents or phototherapy (22).

The roles of specific proinflammatory cytokines that contribute to the disease pathogenesis are clear. Upon activation of plasmacytoid dendritic cells, they produce IFN- $\alpha$ , an activator of myeloid dendritic cells. Together with IFN- $\gamma$ , TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 they produce IL-12 and IL-23. This pathway further activates T helper, Th1 and Th17 cells, which produce IL-17A, IL-17F, and IL-22. The latter activates keratinocytes and many cytokines, initiating an unstoppable proinflammatory cascade (23).

For years, there has been an argument among investigators about whether the primary process in the disease involves the interaction between hyperplastic keratinocytes with secondary immune activation or vice versa. In a clinical trial where T cells were targeted with the DAB389IL-2 agent, denileukin diftitox, which causes the apoptosis of activated T cells, showed that the immune system can play this important role (24). A better understanding of the inflammatory nature of psoriasis and the investigation of the role of proinflammatory cytokines makes the path of treatment dramatically challenging and promising for novel, effective therapies in future (25).

### **From Genomics to Proteomics in Psoriasis: Advantages and the Power of Proteomics Analysis**

Genetic studies including genome-wide association studies (GWASs) are promising for developing new treatment therapies for many diseases, including psoriasis. The first large-scale GWAS for psoriasis genotyped 25,215 single nucleotide polymorphisms (SNPs) and showed that variants at IL12B and IL23R are important factors related to disease susceptibility (26). Specifically, the HLA-C variant in the MHC region, located at 6p21, plays a crucial role. The progression of psoriasis changes the expression of genetic variants, but still a lot of work is needed to explain the disease's heritability. Linkage analysis in familial psoriasis, investigates several loci potentially linked to the disease onset (PSORS1 to PSORS9). While these studies are extremely successful in identifying loci for many diseases, psoriasis, being a multifactorial condition, presents a more difficult identification challenge. Furthermore, of the nine different regions that are most investigated (27), PSORS1, located in the MHC region, explains most of the cases associated with (28) early-onset disease appearance. Human leukocyte antigen (HLA)-C and other alleles such as  $\alpha$ -helical coiled coil rod (HCR) and corneodesmosin (CDSN) (28) seem to correlate with the young onset of disease. However, further investigation is necessary for patients >50 years of age. HLA-Cw6 in PSORS1, and the human leukocyte antigen (HLA) alleles are recognized to play a role in disease susceptibility

(29). HLA-Cw6 can present a specific melanocyte autoantigen, named ADAMTS-like protein 5 to CD8+ T cells (30) and it exhibits a high affinity for LL-37, a T-cell autoantigen found in in psoriasis samples (31, 32).

The importance of proteomic methodologies, including identification and quantification, is evolving. Thus far, very few studies have focused on the proteome level, and global proteomic analysis of psoriasis is not as common as gene expression-based studies. Proteomic analyses comprise a challenging process, due to the diverse range of proteins involved, many of which may be detected in very low concentrations in the investigated plasma or serum. Both plasma and serum potentially have higher protein concentrations compared to other biological samples; specifically, approximately 90% of the total protein consists of albumin and immunoglobulin G (IgG) (33).

The high expression of keratin in keratinocytes and collagen in fibroblasts creates barriers that make difficult the analysis of proteins. These barriers lead to masking effects, making the identification of low abundant proteins quite challenging in serum, plasma, and tissue samples. Sample enrichment strategies have been incorporated into sample preparation methods to address this challenge. Among the most common ones are the fractionation of the cell extract into subcellular environments, or the selective extraction of abundant proteins in sample analysis (albumin, IgGs) mainly by immunodepletion, to isolate specific cellular fractions or enriched the plasma proteome respectively; however, the added value of immunodepleting methods has been of minor significance in most cases. Thus, most studies mainly focus on total proteome analysis (34). During the last decade, different methods such as selective reaction monitoring/multiple reaction monitoring (SRM/MRM) and parallel reaction monitoring (PRM) targeting specific protein molecules have been developed and utilized as validation methods in proteomics studies (35, 36). A typical proteomics workflow includes protein homogenization with a lysis buffer consisting of detergents or chaotropic agents, reduction (of disulphide bonds), alkylation (blocking of the reduced disulphide bonds), and finally digestion of the proteins with enzymes (usually trypsin) to obtain peptides. The tryptic digests are usually cleaned and analysed with liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). In psoriasis, the process of cell regeneration and cell differentiation is highly dysregulated (37). This triggers an immune response, inflammatory cell activation, and finally the involvement of keratinocytes, which play an important role (38, 39). IL-17/IL-22-producing T cells are mostly involved in the initial phase of psoriasis, followed by the regulation of the chronic phase by IFN-producing Th1 and Tc1 cells. The interleukin-1 (IL-1) family of cytokines: such as interleukin-36 (IL-36) cytokine and IL-36 receptor antagonist (IL-36Ra/IL36RN)) are part of the process (40, 41). It is well-established that during progression of this disease, the

concentration of proinflammatory cytokines in the plasma extracted from patients is higher than that in healthy individuals.

Skin and serum samples from patients with psoriasis present a significant over-expression of IL-36 $\alpha$ , IL-36 $\beta$ , and IL-36 $\gamma$  (42). Human serum and plasma are the most commonly investigated samples for protein biomarkers of the disease and treatment response (43). Histopathological analysis of skin specimens is also common but it is invasive and usually cannot be applied to undiagnosed populations unless they present symptoms before being diagnosed. In contrast, the collection and investigation of blood for proteomic analysis and the identification of reference proteins acting as biomarkers are far less invasive approaches.

Two main strategies are applied for the analysis of plasma and serum proteins. The first, termed the “rectangular” strategy, was investigated by Geyer *et al.*, wherein they tried to correlate the proteome patterns of large studies with their expressed phenotypes. This is a screening procedure of the serum or plasma proteomes using mass spectrometry (MS) techniques to analyse many protein samples. The second, known as the “triangular” strategy, compares protein expression between normal and disease samples using technologies that subsequently select specific proteins as “report protein” biomarkers (43, 44). The evaluation of the results is usually performed in validation experiments of different sample cohorts using different immunoassays, such as western blot, ELISA or immunohistochemistry, as well as targeted proteomics analysis, such as SRM/MRM or PRM.

### **Proteomics Research Leads to Novel Biomarkers in Psoriasis**

Research is carried out to examine the differentiation in protein profiles that affect disease pathology. The first comparative analysis in patients with psoriasis, specifically those with plaque psoriasis and acute guttate psoriasis was conducted by Carlen *et al.* (45). They used two-dimensional gel electrophoresis and compared protein expression in lesional and non-lesional skin samples. Eleven differentially expressed proteins were identified totally, with nine proteins with increased and two proteins with decreased expression, in patients with psoriasis compared to the healthy group. Moreover, according to their findings, the changes in skin proteins are mostly identified in patients with long-lasting disease. So far, the investigation of psoriatic proteins with several proteomics technique analysis has revealed the structure and location of many proteins (Table I). Lea *et al.*, in 1958, working with serum, revealed changes in proteins in patients with psoriasis based on electrophoresis (46). More than 1,200 proteins were identified by Lundberg and his team, utilizing preclinical experiments. Proteins such as Stefin A1, Slc25a5 ADP/ATP translocase 2, Hsd17b10 3-hydroxyacyl-CoA dehydrogenase type-2, Serpinb3b, Tgm3

77 kDA protein showed almost >2-fold change in psoriasis compared to healthy skin (41). They reported an increase in proteins serpinB1 (serpinb3b), KLK6, cystatin A (stefin A1), and slc25a5 in patients with psoriasis. The results emphasize the importance of preclinical disease models in research (47). Mouse models and the use of proteomic approaches may assist in the identification of novel therapeutic targets. However, Lowes *et al.* (48) had previously emphasized that the mouse models are not ideal for studying pathogenesis patterns observed in psoriasis in mouse, mainly due to the differences between human and mouse, particularly in immune cell system and epidermis biology.

Proteomics can also play an important role in monitoring diagnosis, treatment efficacy, and drug toxicities. Plavina *et al.* (49) analysed plasma for the isoforms of glycoproteins using multi-lectin affinity chromatography (M-LAC) with nano LC-MS/MS and identified many proteins and peptides to be increased in the peripheral blood of the patients with psoriasis. They compared the M-LAC followed by nano LC-MS/MS used previously (glycoproteome), with classical LC-MS/MS techniques for the total proteome (50), and identified 21 differentially expressed proteins (DEPs). Most of the proteins identified were previously associated with several autoimmune and inflammatory diseases. Although they confirmed consistency between both methods described above, they suggested using both protocols in parallel to increase efficiency instead of relying in one only. The combination of albumin and IgG depletion with M-LAC fractionation, followed by nano LC-MS/MS analysis of digested proteins, and comparative quantitation seems to be the most effective approach. Using label-free quantitation, they could measure many important differences in the proteins of the plasma, at very low concentrations compared to ELISA results. This method is sensitive and important for investigating novel proteins or potential biomarkers (49).

Gegotek *et al.* (51) used a GeLC-MS/MS-based approach to investigate changes in the plasma proteomics of patients with psoriasis. Investigating the differential expression of proteins in the plasma of patients compared to controls, they further matched samples according to sex and age. They noted a significant decrease in the abundance of proteins involved in lipid metabolism, signal transduction or immune response. Their study confirmed the already known results about immune response and role of Vitamin D in the plasma of patients with psoriasis. The added value of this study was the identification of several new DEPs that were involved in signal transduction, lipids, and enzyme activity, shedding light on different pathways of the disease. In another study, Li *et al.* investigated the proteomic profile of peripheral blood mononuclear cells in patients with new onset psoriasis and healthy controls. Authors utilized a tandem mass tag (TMT) labelling approach followed by LC-MS/MS analysis and identified 5,178 proteins among which 4,404 were quantified. Through a cut-off ratio, 335

Table I. Summary of proteomics studies in psoriasis.

Author, year (Ref)	Methodology	Number of samples	Sample	Findings
(Lea <i>et al.</i> , 1958 ) (46)	Electrophoresis	Eighteen patients (13 males, 5 females)	Serum	Different protein expression between healthy and psoriasis patients
(Fattahi <i>et al.</i> , 2014) (53)	2-DE, MALDI-TOF/TOF	10 healthy controls (6 males, 4 females) Twenty patients (10 males, 10 females) 16 healthy controls, (8 males and 8 females)	Serum	Higher expression of $\alpha$ -1-antitrypsin, keratin 10 and identification of a new protein in serum of patients.
(Reindl <i>et al.</i> , 2016) (54)	Label-free, LTQ-OrbitrapnanoLC-MS/MPS (Proteome Discoverer 1.3, SIEVE, MetaboAnalyst)	133 patients (100 patients with psoriasis vulgaris, 33 with psoriatic arthritis)	Plasma	208 proteins with differential levels in patient's plasma
(Matsura <i>et al.</i> , 2017) (55)	MALDI-TOF MS, TripleTOF-MS/MPS	24 samples (psoriasis vulgaris), 10 samples (psoriatic arthritis), 23 samples (healthy)	Serum	Differential expression of many peptides in patients compared to healthy. (fibrinogen $\alpha$ chain-derived peptide, flaggrin-derived peptide)
(Gegotek <i>et al.</i> , 2018) (51)	GeLC-MS/MS	6 patients with psoriasis (3 males and 3 females) and 6 healthy controls	Plasma	Differential expression of proteins involved in lipid metabolism, vitamin D activity, proteins involved in signal transduction and immune response cascade.
Li <i>et al.</i> , 2018) (52)	LC-MS/MS	31 new onset psoriasis patients, 32 healthy controls	Peripheral blood mononuclear cells	Differential expression of proteins involved in activation of immune cells, cellular energy metabolism, proliferation, NF- $\kappa$ B pathway
(Bonnekoh <i>et al.</i> , 2007) (56)	MELC robot technology	6 patients	Skin	Following efalizumab therapy, co-localization of different inflammatory epitopes
(Xu <i>et al.</i> , 2019) (71)	Protein array and MS	23 psoriasis patients (20 male, 3 female) 16 healthy controls (14 males, 2 females)	Serum and plasma	Statistically important high expression Proteins: PI3, TNFRSF8, PFN1, KRT16, TNFSF8, KLK1, APOC3, CXCR3, and CCL4 PI3, CCL22, IL12B expression associated with PASI
(Kolbinger <i>et al.</i> , 2017) (57)	Targeted immunoproteomics	8 male patients, 8 healthy male controls	Serum, skin	High expression of TNFRSF8, CD14 associated with the VAS score Biomarkers: B-defensin 2 for IL-17A. Proinflammatory cytokines dysregulation
(Foulkes <i>et al.</i> , 2019) (58)	RNA sequencing and SOMAscan	10 patients (8 males, 2 females)	Blood, skin, serum	Neutrophil chemo attractants after secukinumab treatment, back to normal TNF-dependent proteins were higher before the treatment with etanercept in psoriasis patients
(Medvedeva <i>et al.</i> , 2020) (59)	Myriad RBM sandwich immunoassay's	526 patients	Plasma	Biomarkers: IL17A, KLK7 associated to disease severity and apremilast pharmacodynamics in psoriasis
(Lamoureux <i>et al.</i> 2011) (61)	SILAC, LC-MALDI-TOF/TOF MS/MS		HEK-293 renal cells	Cyclosporine changed the levels of 60 proteins Partially recovered by N-acetylcysteine

Table I. Continued

Table I. Summary of proteomics studies in psoriasis.

Author, year (Ref)	Methodology	Number of samples	Sample	Findings
(Van Swelm <i>et al.</i> , 2013) (60)	MALDI-TOF MS, LTQ-nanoLC-MS/MPS	60 patients	Urine	Urinary Biomarkers: N-cadherin, inter- $\alpha$ -trypsin inhibitor heavy chain H4, haptoglobin, serotransferrin potentially serving as methotrexate-induced hepatic fibrosis. Eleven differentially expressed proteins were identified totally with higher expression in psoriasis patients.
(Carlen <i>et al.</i> , 2005) (45)	Two-dimensional gel electrophoresis	6 lesional, 5 non lesional acute psoriasis 7 lesional, 3 non lesional chronic psoriasis, 4 healthy controls	Skin	9 proteins with increased expression 2 proteins with decreased expression 1,200 proteins with differentially expressed peptides
(Lundberg <i>et al.</i> , 2015) (47)	KC-Tie2 psoriasis mouse model. Gel-based fractionation & label-free protein expression technique	7 patients 6 healthy controls	Skin	>100 proteins with >2-fold changes comparing lesional to healthy skin (slc25a5, cystatin A, KLK6, erpinB1) 50 differentially expressed proteins Profilin 1y increase
(Williamson <i>et al.</i> , 2013) (62)	Stable isotope dimethyl labelling technique & LTQ-Orbitrap-nanoLC-MS/MS	4 patients	Skin	Potential biomarkers for human skin cell: (LICAM/CD171) (DDP4/CD26)
(Gschwandner <i>et al.</i> , 2017) (63)	GeLC-MS/MS		Skin	

2 DE: 2 Dimensional electrophoresis; MALDI: matrix-assisted laser desorption/ionization; MS: mass spectrometry; TOF MS: time-of-flight mass spectrometry; LC: liquid chromatography; HEK: human embryonic kidney; nanoLC: nano-liquid chromatography.

proteins were up-regulated and 107 were down-regulated. The investigated DEPs, were found to be involved in the activation of immune cells, metabolism, and proliferation. IKK $\beta$ , p50, p65 proteins were up-regulated. Western blotting confirmed the up-regulation of p-IkBa and p-p65 in the NF- $\kappa$ B pathway, indicating its significant involvement in psoriasis. However, there were also several DEPs that have never been previously associated with psoriasis, warranting further investigation (52). LC-MS/MS seems to be superior to 2D gel MALDI-TOF MS in terms of protein identification and resolution. This is mainly why almost only LC-MS/MS is highly utilized today. Nevertheless, in 2014, Fattahi *et al.* (53) using the MALDI/TOF-TOF technology, found that retinol-binding protein is decreased (RBP4) in patients' blood compared to the blood of healthy individuals, whereas KRT10 was higher. Furthermore, they introduced two new isoforms of  $\alpha$ 1-antitrypsin/SERPINA1. Reindl *et al.* (54) using the LTQ-Orbitrap-nanoLC-MS/MS platform, investigated the expression of proteins in the plasma samples and identified 208 DEPs, with complement C3, Zn- $\alpha$ 2-glycoprotein/AZGP1, polymeric immunoglobulin receptor/PIGR, and plasma kallikrein/KLK6 differing between patients and healthy individuals. Matsuura *et al.* (55) using MALDI-TOF MS and Triple-TOF MS/MS, compared the blood serum of patients with psoriasis, psoriatic arthritis, and atopic dermatitis and identified 93 DEPs, with many of them comprising parts of four proteins: fibrinogen  $\alpha$ /FGA, filaggrin/FLG, thymosin beta-4/TMSB4X, and FLJ55606.

### Novel Biomarkers to Specific Therapy

Bonnekoh *et al.* (56) used a multi-epitope ligand cartography (MELC), which utilizes an array of specific antibodies, to investigate biomarkers of therapeutic response to efalizumab and evaluate prognostic factors for treatment efficiency. CD45, CD2, CD4, and CD8 levels were decreased in responders, which may be an indication that these DEPs are associated with the appearance of leukocytes and T-cells sub-populations. In another study, 170 proteins were investigated regarding their expression in the blood and skin of patients with psoriasis and healthy individuals, before and after treatment with the anti-IL17A monoclonal antibody, secukinumab (57). They used the proximity extension assay (PEA) and found that the expression of many antimicrobial peptides and proinflammatory cytokines was highly increased, which normalized after treatment with secukinumab. Foulkes *et al.* (58) used SomaScan and found a higher expression of TNF-dependent-proteins in the blood of patients with psoriasis before treatment with etanercept.

SomaScan was utilised in a large study (59) focusing on the use of apremilast, a specific inhibitor of phosphodiesterase 4 (PDE4). The study included corresponding analyses from placebo-controlled Phase III clinical trials of apremilast in

psoriasis, psoriatic arthritis, and ankylosing spondylitis involving 526 subjects. IL-17A and KLK-7 were identified as biomarkers, and the role of the drug in the treatment was evaluated. Four DEPs: KLK7, PEDF, MDC, ANGPTL4, were found to be decreased in responders compared to non-responders to apremilast. According to the findings, it might be optimal to use the combined expression KLK7, PEDF, MDC, and ANGPTL4 in the blood in order to identify responders to the drug.

Long-term use of conventional drugs for psoriasis, such as methotrexate and cyclosporin, present many adverse events, especially toxicities. Several attempts are underway to identify novel biomarkers using proteomics. Van Swelm *et al.* (60) investigated the urinary biomarkers for methotrexate-associated hepatic adverse events with MALDI-TOF MS and LC-MS/MS. Sixty psoriatic urine samples, from patients treated with low-dose dose methotrexate, were collected, and the study found that proteins, such as N-cadherin, haptoglobin, serotransferrin as potential predictive urinary biomarkers for methotrexate-related toxicities. However, the reliability of these biomarkers may need confirmation through liver biopsy and other methods, according to the findings of the study.

Cyclosporine, on the other hand, is another drug used for the treatment of psoriasis. Lamoureux *et al.* (61) using the cell culture labelling stable isotope (SILAC) technique, followed by LC-MALDI-TOF/TOF MS/MS, investigated the effects of cyclosporine on renal proteomics features. They found that 69 proteins were highly altered by cyclosporine, with many involved in stress response, protein folding, apoptosis, transport, and cytoskeletal regulation. The question that arises is whether these renal proteins can be potential biomarkers for cyclosporine-related nephrotoxicity. Further investigation may reveal whether these altered protein expressions could be the beginning of a cascade of protein expression changes indicative of nephrotoxicity.

Williamson *et al.* (62), through a quantitative proteomics technique, using a stable isotope dimethyl labelling and LC-MS/MS, investigated 50 DEPs, and monitored changes in the levels of lysozyme C, profilin 1, neutrophil gelatinase-associated lipocalin (NGAL) in the plasma using mass spectrometry (SRM-MS/MS). They found that only profilin 1 was increased in the psoriatic plasma, suggesting that it could serve as a candidate biomarker. Gschwandtner *et al.* (63), using the label-free quantitative proteomics technique GeLC-MS/MS in mast cell proteins and comparing them with other skin cells, found two proteins, the neural cell adhesion molecule L1 (L1CAM/CD171) and dipeptidyl peptidase 4 (DDP4/CD26), which could potentially serve as biomarkers for human skin mast cells in normal, psoriatic, and mastocytosis skin. However, we cannot yet predict the treatment response of psoriasis biology in individual patients, particularly as the timepoint of the biological response

remains undetectable. Transcriptomic analysis could help us predict the effects and responses of drugs, facilitating effective treatment by enabling investigators to closely monitor biological to clinical responses. Rosa *et al.* (64) has shown that data from gene expression analysis of lesional skin in the first four weeks of treatment with drugs, such as Etanercept, Ustekinumab, Adalimumab, and Methotrexate, could predict the clinical outcome by week 12. This could reduce the evaluation gap between biological and clinical responses by at least two months.

### Protein Microarrays

Considering post-translational modifications, the final proteins produced are more heterogenous than the genes encoding them. Proteins are differentially produced in diseases and proteomics analyses is a tool that could support the improvement of our understanding of diseases, contributing to individualized therapy. The analysis of protein panels could help us understand the disease development and aid diagnosis, using multiplex techniques to screen proteins from small sample amounts. Biologic therapy, over the long term, increases the effectiveness of treating patients with moderate to severe forms of the disease (65). In terms of precision medicine, patients respond better to the prescribed drug, improving the initial response rate while reducing cost. As already mentioned, microarray-based studies in psoriasis have revealed many differentially expressed genes (DEGs) (66). Protein microarray technology, which started right after the DNA microarray technology, and the current studies have significantly contributed to investigating alterations in gene expression within cells. Similarly, protein microarrays have been developed to study proteins, peptides, antibodies and their differential expression (67), facilitating the quantification of candidate biomarkers from large numbers of samples analysed at the same time.

Multiplex protein assays are expected to advance and find applications in future diagnostic areas. Depending on their application, protein microarrays can be analytical or functional. Analytical tests use antibodies for qualitative and quantitative analysis (68). Functional tests, on the other hand, are important for uncovering interactions between proteins and other molecules, such as DNA, other proteins, lipids, or drugs (69). Various types of protein microarrays exist, including forward-phase protein microarray (FPPM) and reversed-phase protein microarray (RPPM) that could maximise testing capabilities. These enable the analysis of a large number of different parameters in a sample or a large number of different samples, immobilized as spots. Protein microarrays hold significant potential for biomarker investigation, especially RPPMs, which could identify biomarker candidates in cancer patients (70).

Further advances in protein microarray technology could enable investigators to use a simple drop of blood to screen patients for relevant pathologies before prescribing drugs. Using protein arrays with specific antibodies to disease-associated protein biomarkers, a large number of proteins associated with disease onset can be identified. Quantitative assessments could then be used to evaluate the intensity of the disease (71).

## Conclusion

During the last decade, a wide range of proteomics methodologies has been applied to obtain data on new mechanisms underlying disease pathogenesis, with a focus on biomarkers identification for prognosis, diagnosis and enhancing treatment efficacy. The goal is to identify proteins that play a role in psoriasis manifestations and provide targeted therapy to patients in the early phase of their disease. The notion of treating patients on an individual basis may be closer than previously thought, thanks to the transformative impact of ‘omics’ technologies on disease investigation. Proteomics is still in its early stages, and there is a need for larger studies that will ideally combine proteomic techniques with other technologies. This approach will allow for a deeper understanding of disease mechanisms and the development of new therapeutic interventions that are more effective and have fewer toxicities.

## Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

## Authors’ Contributions

GL and MK were responsible for conceptualization and writing. All Authors have reviewed and edited the paper. All Authors have read and agreed to the published version of the manuscript.

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